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Archives of Internal Medicine

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HARMFUL EFFECTS OF SHALLOW BREATHING WITH SPECIAL REFERENCE TO PNEUMONIA*

JONATHAN MEAKINS, M.D.

MONTREAL

It has been demonstated by Haldane, Meakins and Priestley[1] that abnormal shallowness of the respirations produces anoxemia. This is demonstrated by the occurrence of periodic breathing, cyanosis and other symptoms indicative of this condition.

The manner in which this abnormal type of breathing produces the anoxemia has also received considerable attention from them. Keith has demonstrated that the lungs do not expand after the manner of the bladder when external pressure is reduced, but like a Japanese fan. He has also pointed out that expansion of the lungs does not take place constantly and uniformly throughout. Therefore this type of breathing would of necessity exaggerate the uneven distribution of air to the alveoli.

They also found that the expired air and the alveolar air in cases exhibiting this type of respiration contained a large percentage of oxygen, which rendered it difficult to reconcile this condition with a pronounced anoxemia.

The circulation of blood through the different parts of the lungs is fairly uniform. As a consequence of the irregular expansion of the lungs, some part of the blood would be oxygenated well in the well ventilated parts, while some blood would be oxygenated poorly in the poorly ventilated parts, with the result that the arterial blood going to the heart would be a mixture of these two bloods, and depending on the shallowness of the breathing, the mixed arterial blood would obtain a greater or less amount of oxygen.

Reference to the dissociation curves of oxygen and carbon dioxid furnishes additional evidence as to how such a condition of anoxemia with high oxygen in the mixed alveolar air may occur. It is possible for the diminished removal of carbon dioxid from the poorly ventilated parts of the lungs to be compensated for by increased removal of

* Read before the Association for the Advancement of Clinical Investigation, Atlantic City, June 14, 1919.

1. Haldane, Meakins and Priestly: J. Physiol. **52**:444 (May) 1919.

carbon dioxid by the well ventilated parts. Thus the carbon dioxid tension of the mixed arterial blood remains at a normal level. But in regard to the oxygen, it is totally different. "In the badly ventilated parts of the lung the volume of blood flowing per minute will be greater in relation to the amount of fresh air entering these parts than in the well ventilated regions. Hence, the blood will take up more of the oxygen and the percentage of oxygen in the relatively stagnant alveolar air of the badly ventilated parts will fall below the average. The dissociaton curve of blood for oxygen is totally different from the carbon dioxid curve, and as the oxygen in the stagnant air falls, the percentage saturation of the blood passing through these alveoli must also fall greatly. But for oxygen pressures above about 88 mm. Hg the curve is very flat. Hence, any increase of ventilation beyond the amount sufficient to keep the alveolar carbon dioxid at this level is quite unable to add appreciably to the amount of oxygen taken up by the blood. Thus it follows that in the well ventilated parts of the lungs first the increased ventilation is incapable of yielding an excess of oxygen to the blood sufficient to compensate for the lack of oxygen in the blood from the badly ventilated parts, and second, since more than the average amount of fresh air is passing through these alveoli, while no more than the normal amount of oxygen is being absorbed by the blood, the air expired from these well ventilated alveoli must be abnormally rich in oxygen. Thus the average composition of the alveolar air may remain constant as regards percentage of oxygen, as is normally the case, or, when the breathing is abnormally shallow, the oxygen content of the average alveolar air may rise above the normal level even though at the same time the arterial blood is inadequately supplied with oxygen."

The same authors have further pointed out that one of the respiratory responses to anoxemia is the occurrence of frequent and correspondingly shallow breathing.[2] Thus under certain circumstances it is quite conceivable that a vicious circle might be established.

These observations on shallow breathing resulted from an investigation of certain cases of "irritable heart" and "suffocative gas poisoning." But there are other cases of great clinical importance in which this same condition is found. The most important is pneumonia. It is a well known clinical observation that the severity of the symptoms in a case of pneumonia is not necessarily dependent on the degree of pulmonary involvement. A much more valuable indication as to the prognosis of the disease is the respiratory rate. It has been observed that as the respiratory rate increases the patient's condition becomes

2. Haldane, Meakins and Priestly: J. Physiol. **52**:420 (May) 1919.

more grave. The point at which alarming symptoms develop varies in different individuals. But, as a rule, in adults when the respiratory rate persists above 50 per minute cyanosis begins to develop. This is a definite sign of pronounced anoxemia.

The harmful effect of persistent anoxemia on the cardiovascular system is well recognized. Of the fact that the cyanosis in cases of pneumonia is due to cardiovascular failure there is no definite proof. Careful observation, however, will reveal the fact that the cardiovascular collapse is a sequel of the anoxemia.

If the respiratory rate continues with sufficient rapidity and shallowness to produce persistent cyanosis, the cardiovascular system begins to show signs of failure, such as pronounced increase of pulse rate, gradual lowering of blood pressure with eventual collapse, the patient showing the "gray cyanosis" and other symptoms of "shock."

A number of cases of pneumonina have been investigated in order to determine the quantity and quality of the expired air. For obvious reasons it was impossible to obtain the alveolar air in such cases. It was found that as the respiratory rate increased, there was a gradual decrease in the volume per respiration, but the total ventilation per minute showed a conspicuous increase.

On referring to Table 1 these points will be observed. It will be noted also that, although the total volume per minute of expired air gradually increased, there is a very conspicuous diminution in the ratio between the volume of each respiration and the theoretical dead space. This latter we may presume remains fairly constant in each individual case. Therefore, the point may be reached where the alveolar air, expired or inspired, amounts to a comparatively few cubic centimeters, being undoubtedly insufficient to carry on any adequate pulmonary ventilation, so that eventually cyanosis develops.

The respiratory quotient becomes progressively higher, at times it may reach 1.2, but when the crisis occurs there is a rapid return to normal not only in regard to the respiratory quotient, but also in so far as the respiratory rate, respiratory volume and total ventilation per minute are concerned. It is not probable that this is due to any conspicuous change in the damaged lung, as all means of ordinary examination go to indicate that several days must elapse before such change is appreciable. Furthermore, it is common knowledge that practically one half of the lung area may be nonfunctionating (artificial or spontaneous complete pneumothorax) without producing, while at rest, any evident respiratory distress.

There is another aspect of this question which must be considered, namely, the part played by the pulmonary circulation. Until recently it was not known to what extent the pulmonary circulation was inter-

TABLE 1.—Quantity and Quality of Expired Air in Pneumonia

No.	Day of Disease	Pulse Rate	Temperature	Cyanosis	Respiration per Minute	Volume per Respiration, C.c.	Volume per Minute in Liters	Expired Air			Barometric Pressure	Result	Remarks
								Oxygen, per Cent.	Carbon Dioxid, per Cent.	Respiratory Quotient			
1	2	100	103.6	0	58	310	11.78	18.14	2.46	0.88	758	.....	Right lower lobe involved
	4	104	104.4	0	45	270	12.15	18.20	2.43	0.86	752		
	6	120	104.2	+	54	230	12.42	18.84	2.14	1.01	763		
	7	140	104.6	++	60	210	12.60	19.13	2.00	1.11	757	Died	
2	3	106	104.4	0	42	300	12.60	17.89	2.86	0.91	755	.....	Right lower and middle lobes involved
	5	110	104.0	0	44	294	12.93	17.96	2.76	0.87	754		
	6	108	104.2	0	45	290	12.75	17.98	2.83	0.93	762		
	7	100	98.0	0	34	330	11.22	17.40	3.24	0.88	758	Crisis	
	8	80	98.4	0	24	420	10.08	17.14	3.29	0.85	757		
	9	84	98.2	0	18	505	9.09	17.04	3.58	0.86	758	Cured	
3	4	110	103.4	0	40	300	12.00	17.76	2.79	0.83	759	.....	Left upper lobe involved
	6	108	104.1	0	42	286	11.91	17.94	2.82	0.91	756		
	7	104	104.3	0	45	270	12.15	18.01	2.84	0.94	748		
	8	110	104.4	+	52	240	12.48	18.56	2.36	0.98	755		
	8	124	102.3	++	54	232	12.52	18.83	2.18	1.03	766		
	9	130	103.2	++	64	188	12.03	19.01	2.10	1.09	762		
	9	146	101.0	+++	60	160	10.56	19.30	1.96	1.23	761	Died	
4	4	120	104.2	+	54	220	11.88	18.64	2.32	0.99	740	.....	Right upper and left lower lobes involved
	5	132	104.1	++	52	225	11.70	18.50	2.38	0.95	748		
	6	120	104.2	+	48	230	11.40	18.41	2.45	0.94	746		
	7	110	100.0	0	40	260	10.40	17.95	2.87	0.94	754		
	8	100	98.0	0	28	350	9.80	17.53	3.06	0.81	760	Crisis	
	10	80	97.4	0	18	510	9.18	17.01	3.40	0.85	762	Cured	

fered with in pneumonia. Gross[3] demonstrated that in pneumonia varying degrees of vascular obliteration may occur depending upon the stage of pulmonary consolidation. In the stage of red hepatization there is a moderate preservation of the circulation, but there exist unusual clear spaces with poor injection, and even the injected vessels are somewhat narrowed and compressed. In gray hepatization there is a general lack of injection, only several large branches moderately compressed may appear. These injected branches end abruptly and the whole area of gray hepatization presents a striking anemic condition.

It must be assumed that a certain volume of blood passes through the damaged lung area without being ventilated properly. But it is not warranted to suppose that this nonventilated blood is sufficient in amount to reduce appreciably the oxygen content of the mixed blood entering the left side of the heart.

This conclusion seems justified, therefore, that the anoxemia occurring in acute lobar pneumonia is the result of the rapid and shallow breathing typical of this condition.

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3. Gross: Canad. M. A. J. 9:632 (July) 1919.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

LII. STUDIES ON GASTRIC ULCER *

A. C. IVY, PH.D.

CHICAGO

The studies on gastric ulcer as presented here are the first of a series of studies on the pathologic physiology of the stomach and duodenum in the condition of ulcer of these parts of the gastrointestinal tract.

I. THE OCCURENCE OF ULCER AND OTHER PATHOLOGIC LESIONS IN THE STOMACH AND THE DUODENUM OF THE DOG AS JUDGED FROM ONE THOUSAND NECROPSIES

In a series of studies to be made on a pathologic physiologic condition it is obviously essential to make a study of the frequency of the occurrence of that condition in the animal used. A large amount of work has been done on gastric ulcer in which the dog has been the chief experimental animal. There are only two reports in the literature concerning the frequency of the occurrence of ulcer in the dog. Turck[1] reports a series of necropsies on 189 healthy and 82 diseased dogs in which the findings of "peptic ulcer" were absolutely negative. Other pathologic lesions, if they occurred, are not reported. Mann[2] reports a series of more than two hundred normal dogs and cats in which no "lesion of the gastric mucosa was found at necropsy." From the findings of these two observers one might conclude that the occurrence of lesions of the gastric mucous membrane of the dog are very rare. Since the data offered in the literature is meager, it was considered important to ascertain more completely the occurrence of lesions of the gastric mucous membrane in the dog.

METHODS

The stomach and duodenum of healthy, diseased and experimental dogs was removed immediately after death and placed in cold running water where they were examined immediately, or always within one hour after removal. Quite a number of stomachs were examined a

* From the Hull Physiological Laboratory of the University of Chicago.

1. Turck, F. B.: J. A. M. A. **67**:1784 (Dec. 9) 1916.
2. Mann, F. C.: J. Exper. M. **23**:203 (Feb.) 1916.

longer period after death than one hour, but observations on these were not recorded because of the possibility that any lesion present might be the effect of autodigestion.

The lesions observed were classified as follows: (1) Petechial hemorrhage, applied to the condition in which the red blood corpuscles are abundantly packed in the tissues of the mucosa and lie in the mucosa adjacent to the lumen; (2) superficial hemorrhagic erosion, applied to the condition in which there is an evident petechial hemorrhage accompanied by a superficial erosion of the cells of the mucous membrane; (3) acute ulcer, applied to the condition in which there is a well defined break in the continuity of the mucous membrane; (4) chronic ulcer, applied to the condition in which the edges of the ulcer are raised, undermined and thickened, and the base of the ulcer indurated; (5) diffuse inflammation, applied to the condition generally referred to as gastritis in which there occurs a swelling and hyperemia of the mucous membrane together with the production of a viscid adhesive mucus exudate and in acute cases with the occurrence of petechial hemorrhages and superficial erosions; (6) and tumors involving the mucosa. I agree with Bolton[3] that it is neither useful nor correct to call a superficial hemorrhagic erosion an ulcer.

RESULTS

Table 1 shows the occurrence of pathologic lesions in the stomach and duodenum of healthy dogs that had been subjected to ether anesthesia for a period of two or three hours, while students used them for acute laboratory experimentation.

TABLE 1.—SHOWING LESIONS OF THE STOMACH AND DUODENUM (900 DOGS)

Lesions	Cardia		Fundus		Pylorus		Duodenum		Remarks
	No.	%	No.	%	No.	%	No.	%	
Petechial hemorrhages	11	1.2	..	....	26	2.9	13	1.4	
Superficial hemorrhagic erosions	1	0.09	1	0.09	23	2.5	6	0.6	
Acute ulcer	..	....	..	....	1	0.09	..	....	Old emaciated dog
Diffuse inflammation	..	....	4	0.44	4	0.44	22	2.5	
Tumors	..	....	..	....	3	0.33	..	....	Adenomatous polyps

The petechial hemorrhages and hemorrhagic erosions occurred chiefly in the last 2 inches of the pyloric portion of the stomach and in the first inch of the duodenum. In the case of the acute ulcer of the pyloric portion of the stomach there were two ulcers (2 by 1 mm.), involving the entire thickness of the mucosa within one-half inch of the sphincter. The stomach was taken from on old emaciated

3. Bolton: Quart. J. Med. **5**:434, 1911.

animal. No apparent cause for the gastritis could be found. Worms accompanied the enteritis in all except five animals, and may have been the cause in most cases.[4]

TABLE 2.—Lesions Occurring in Thyroid Parathyroidectomized Dogs (Twenty-Four Dogs)*

Stomach	Stomach, No.	Duodenum, No.
Petechial hemorrhages	16	20
Superficial hemorrhagic erosions	13	15
Acute ulcer	1	3
Diffuse inflammation	0	18

* One acute ulcer, 15 × 3 mm., almost perforated was found in the fundus. Otherwise all the lesions in the stomach were confined to the pyloric portion.

Table 2 shows the occurence of ulcer and of lesions of the mucous membrane of the stomach and duodenum in animals dying of thyroid parathyroidectomy. The paramount symptom that was manifested in the animals was depression, as reported by Carlson,[5] only 60 per cent. of them showing tetany. These animals lived from three to twenty days. The severity of the intestinal findings was directly portional in most cases to the longevity of life following the operation.

Eight out of forty dogs dying of distemper (snuffles) showed petechial hemorrhages and superficial hemorrhagic erosions of the pyloric and duodenal mucous membrane. Acute gastritis and enteritis was present in every dog in this series. Hypoacidity is a constant occurrence in these animals. I have seen several cases in which raw meat would pass through the gastro-intestinal tract of a dog sick with distemper without being changed in color. Diarrhea is also present in practically every case, as is anorexia and emaciation.

In ten dogs dying of shock and symptoms of raised intracranial pressure following cerebral ablations, every one showed petechial hemorrhages and superficial erosions of the fundic and pyloric mucous membrane. In four of these dogs the stomach was acutely dilated. No free acid was present in the stomach of these animals.

Out of twenty dogs that had been injected intravenously with ether twenty-four hours previous to death, five showed petechial hemorrhages and superficial erosions of the fundic and pyloric mucous membrane.

Superficial hemorrhagic erosions occur frequently in dogs dying of experimental diabetes.

A deeply eroded and indurated ulcer (4 by 6 mm.), typically chronic, was found in the first quarter of an inch of the duodenum

4. Food was present in the stomachs of about one half of the animals. The lesions had no relation to the presence of food, however.

5. Carlson, A. J.: Am. J. Physiol. **30**: 1912.

in a cachectic dog whose pancreatic ducts had been ligated five months previously and who had been kept on a diet of bread and milk. Hypoacidity was present in this dog. The dog died of acute stomatitis accompanied by rapid emaciation. The stomach and duodenum of twenty-four dogs, in which the pancreatic ducts had been ligated, were examined without finding ulcer. Four of these animals showed superficial erosions. In these dogs emaciation was marked and they died of distemper. The other animals were killed in other experiments, no lesions being present. With the exception of six of these animals, the pancreas was from macroscopic appearance atrophic and fibrotic. Jona[6] reports the presence of ulcers in the duodenum and small intestine following ligation of one pancreatic duct. From his picture and his description, I am led to believe that what he called ulcers were nothing more than Peyer's patches, which occur in the duodeum of the dog, made more conspicuous by emaciation and postmortem digestion. These patches are easily mistaken for ulcers, if a microscopic study is not made.

My observations on suprarenalectomized animals partly confirm those of Mann.[2] In forty suprarenalectomized dogs I have only seen one acute ulcer and twenty instances of petechial hemorrhage and hemorrhagic erosion of the gastric and duodenal mucous membrane, which is less frequent than reported by Mann.

Dogs dying immediately after section of the vagi and splanchnics not infrequently show petechial hemorrhages of the pyloric and duodenal mucous membrane. But in ten dogs that died or were killed from one week to four months following double vagotomy and splanchnotomy with extirpation of the celiac plexus, no gastric or duodenal lesions were found. Durante[7] reports that he observed lesions that were similiar to acute and chronic ulcers in man. He does not state how long the ulcers were present and only states that such animals survive a short time. Most of my animals lived indefinitely and the nerve sections were verified at necropsy. Such animals become cachectic, however, and have to be cared for rather carefully for some time in order to keep them in a normal state of health.[8]

In a personal communication from Dr. S. A. Mathews, I was told that in Eck fistula dogs, which are kept alive for a long period on a diet of bread and milk and which are emaciated and cachectic, chronic ulcers of the stomach are frequently found.

6. Jona, J. L.: M. J. Australia **1**:316 (April 19) 1919.

7. Durante, L.: Surg., Gyn., Obst. **22**:399 (April) 1916.

8. In an emaciated dog with gastrostomy and both splanchnics cut, Dr. A. B. Luckhardt found a chronic ulcer about one inch from the gastrostomy. The ulcer was about to perforate.

The three tumor formations found were adenomatous polyps which were confined in each case to the mucosa of the pyloric portion of the stomach.

No scars were found in the stomach or duodenal mucous membrane. These were looked for as probable evidence of healed acute ulcers. Such scars are reported to occur frequently in man.

SUMMARY AND DISCUSSION

It is apparent from the results of this study that chronic ulcer of the stomach and duodenum in healthy dogs and even diseased dogs, if it occurs at all, is very rare. In diseased and cachectic experimental animals only two marked ulcerations were found: one, very acute and almost perforating, the second, typically chronic. On the other hand, petechial hemorrhages and superficial hemorrhagic erosions do occur in the gastric and duodenal mucosa of the healthy dog. (I have seen them in the mucosa of the stomach even though the animal had not been subjected to ether anesthesia previously.) These lesions, however, occur more frequently in experimental, diseased and cachetic animals.

Comparing these observations with those reported to occur in man, it is seen that the dog is much less subject to gastric lesions than man. According to Adami[9] "hemorrhages into the stomach wall are quite common" in man, and Birch-Hirschfield[10] reports that they are found in 50 per cent. of cadavers. Osler[11] states that hemorrhagic erosions are common. Chronic ulcer occurs in man as often as from 2 to 4 per cent. Why there is such a difference between man and dog is a matter open for speculation. If gastric juice digestion was a basic factor, we would expect more ulcers in the dog than in man as the dog's acidity is on the average greater than man's. The dog being an animal generally of higher resistance and less subject to dietary, toxic and nervous factors, which cause gastric disturbance of motor, secretory and circulatory activity, than man, we would expect to find fewer ulcers. The dog not being so subject to focal infections and hemorrhagic erosions as man, the dog would be less likely to have an ulcer hematogenous in origin. Also, the dog being less subject to nervous influences, which cause hypomotility and hyposecretion, there would be less chance to infect a point of lowered resistance, a petechial hemorrhage or erosion, by bacteria swallowed. These observations

9. Adami, J.: Principles of Pathology, Philadelphia, Lea & Febiger, 1911, **2**: 414.

10. Birch-Hirschfeld: loc. cit., Adami.

11. Osler, W.: The Principles and Practice of Medicine, New York, D. Appleton & Co., 1916, pp. 490, 447, 480.

suggest at least that there is some factor present in man causing the chronicity of the ulcer which is absent in the dog; also, that if chronic ulcer can be produced in the dog's stomach or duodenum, it can be produced in man by the same method.

The fact that chronic gastric ulcer does not occur and that gastric carcinoma is not found in the dog is comparative evidence, I take it, in favor of Mayo Robson's[12] theory of the etiology of carcinoma of the stomach in man. Mayo Robson suggested that gastric ulcer was the source of gastric carcinoma. Wilson and McCarthy[13] have presented evidence in support of this theory.

2. The Experimental Production of Chronic Gastric Ulcer in the Dog

Petechial hemorrhages, superficial hemorrhagic erosions and acute ulcers have been produced experimentally in many ways: mechanically, chemically, by heat, drugs, toxins, peptones, serums, by section of the vagi and the splanchnics, by embolism and thrombosis, anemia, by feeding bacteria, by the intravenous injection of specific and nonspecific bacteria, by abrasions, by lesions to the central nervous system, by removal of the suprarenals and parathyroids, and by many other methods. In other words, they are produced by anything that causes a local necrosis of the membrane by direct toxic or chemical action on the mucosal cells or by interfering or disturbing the normal condition of the capillaries of the mucosa. All biologic methods of producing the hemorrhages seem to point toward a marked susceptibility of the gastric and duodenal mucosal capillaries to injury by toxic and nervous influences.

Although acute ulcers have been produced in many ways, few investigators have claimed to have produced chronic ulcers of the gastric and duodenal mucosa. Bolton[14] and Friedman and Hamburger[15] were able to delay the healing of experimental acute ulcers by producing partial pyloric stenosis. Turk[1] reported that he was able to produce perforating ulcers of the duodenum and stomach by feeding *B. coli*. Durante,[7] by ligating and cutting the splanchnic nerves, reports the production of chronic ulcers. Rosenow[16] has reported the production of gastric and duodenal ulcers that "resemble those in man in location and tend to become chronic, to perforate and to cause hemorrhage" by the intravenous injection of alleged specific streptococci.

12. Robson, A. W. M.: Lancet **2**:1547, 1904.
13. Wilson, L., and McCarthy, W. C.: Am. J. M. Sc., 846 (Dec.) 1909.
14. Bolton: Proc. Roy. Soc., Lond. **82**:236, 1909.
15. Friedman, J. C., and Hamburger, W. W.: J. A. M. A. **62**:380 (Aug. 1) 1914.
16. Rosenow, E. C.: J. Infect. Dis. **19**:333 (Sept.) 1916.

The chief views held at the present time concerning the etiology of chronic gastric ulcer are as follows: (1) Infection of the mucous membrane through the blood by specific or nonspecific bacteria from a focal infection is the primary factor and the source of reinfection; (2) the digestive action of the gastric juice on mucosal cells that have had their normal resistance to acid peptic digestion diminished in some way; (3) a localized trophic disturbance is responsible for the chronicity of the ulcer; (4) the infection of the mucous membrane by swallowed bacteria.

Most investigators in this field agree with Bolton[17] that chronic ulcer originates from an acute lesion and that most of the acute lesions heal rapidly.

This study was undertaken as an attempt to throw more light on the experimental production of chronic ulcer in the dog.

METHODS AND RESULTS

Healing of Experimental Acute Ulcers.—The time required for the healing of acute ulcer produced by Roth's method (the injection submucously of 1.0 c.c. of a 5 per cent. silver nitrate solution) in the fundic and pyloric portions of the stomach and in the duodenum. Ulcers made in the mucous membrane of the fundic portion of the stomach healed in from nine to thirteen days; when ulcers were made in the pyloric portion of the stomach, healing required from twelve to eighteen days; if the dogs had the distemper, healing required from eighteen to twenty-two days. In the duodenum from sixteen to twenty-four days were required for the healing of the ulcer.

This difference in the rate of healing is explained, I believe, by the anatomy and physiology of the different portions and the way in which ulcers of the mucosa heal. The manner of healing has been described in detail by Bolton[14] and Griffini and Vassale.[18]

Aseptic Embolism.—Injections of finely divided animal charcoal suspensions were made into the branches of the gastro-epiploic arteries with negative results. Suspensions of lead chromate and pigments were injected into branches of the gastro-epiploic arteries with resulting petechial hemorrhages and hemorrhagic erosions. Acute ulcers resulted in three of the animals injected with lead chromate. The results with lead chromate and pigments confirm the observations of Cohnheim[19] and Klebs and Welti.[20] Why the injection of animal charcoal gave negative results cannot be stated. The findings suggest

17. Bolton: Ulcer of the Stomach, London, 1913.
18. Griffini and Vassale: Ziegler's Beitr. **3**:425.
19. Cohnheim: Lect. on Gen. Path. (New Sydenham Soc.) **3**:878, 1890.
20. Klebs and Welti: Handb. d. path. Anat., 1869.

that effects produced by pigments and lead may be toxic and that an embolism produced by an inert, nontoxic substance, charcoal, will not result in hemorrhage or acute ulcer.

Ligation of Blood Supply.—Six to eight of the branches of the gastro-epiploic vessels supplying the pyloric portion of the stomach were ligated with negative results. This confirms the results of Littauer[21] who found that the blood supply to one third of the stomach could be cut off without producing dileterious effects and demonstrates a marked freedom of anastomosis.

Silver nitrate ulcers were made in such an area to which the large blood vessels had been ligated with the result that they healed in normal time. The ulcers were made at the same time that the vessels were ligated.

Partial Pyloric Stenosis and Healing of the Ulcer.—The effect of partial pyloric stenosis on the rate of the healing of the ulcer was studied in eight dogs. In five the healing time of the ulcer was delayed from two to four weeks. No marked induration of the edges occurred in any case. The ulcers in the three dogs which did not manifest rapid loss of weight healed in normal time. To ascertain the condition of the ulcer, the dog was killed in some cases, in other cases operated on aseptically and the ulcer examined by direct inspection through an incision in the stomach wall. These findings confirm the observations of Bolton[14] and Friedman and Hamburger,[15] who report delayed healing in acute experimental ulcers accompanied by partial pyloric stenosis. Bolton reports delayed healing only, while Friedman reports a chronic ulcer at eight weeks after the production of the acute ulcer. Bolton accounts for the delayed healing as "due to necrosis of the base of the ulcer or excessive formation of sclerotic tissue therein, such conditions being the result of the low resistance which the connective tissues possess to digestion by gastric juice, or possibly in some cases to a secondary bacterial infection." Friedman and Hamburger account for the delayed healing by the prolonged action of the gastric juice and hyperperistalsis. Loss of weight and disturbed nutrition, which I observed in my animals and which is reported by both of the above investigators, although not emphasized, and bacterial infection of the acute ulcer must also be considered as possible factors in the delayed healing following partial pyloric stenosis.

Injections of Bacteria.—Injections of streptococci (one tube of a twenty-four-hours-old culture in dextrose ascites broth) were made into two or three branches of the gastro-epiploic arteries in a series of

21. Littauer: Virch. Arch. **195**: No. 2, 328.

dogs with negative results. The dogs were killed from two to four weeks after the injection, so if any acute effects were produced, they did not persist nor leave scars. In two dogs killed twenty-four hours after the operation petechial hemorrhages were found. Perigastritis resulted in every case. Two strains of streptococci were used, one a *Streptococcus viridans* isolated from a tonsil, the other a *Streptococcus hemolyticus* from a case of septicemia. Dr. Clawson of the department of bacteriology, from whom the bacteria were obtained, stated that both were fatal for rabbits. The *S. viridans* when injected (three tubes of a twenty-four-hours-old culture of dextrose ascites broth) into dogs caused no symptoms; the *S. hemolyticus* when injected into dogs caused a rise in temperature, inactivity and loss of appetite of three days' duration. Although the bacteria were virulent enough to produce a dense fibrinous and fibrous perigastritis at the site of injection, no acute ulcers of the stomach resulted. These results suggest that either a markedly virulent or a specific bacterium is required to produce an acute ulcer of the stomach. I have injected streptococci beneath the skin and the mucosa of the stomach at the same time and in the same dog; in the former instance an abscess developed, while nothing resulted from the submucosal injection.

Feeding Bacteria.—The effect of feeding bacteria to dogs in which an experimental abrasion of the pyloric and duodenal mucous membrane had been made was studied. The laceration was made under aseptic procedure through an incision in the anterior wall of the stomach by pinching and tearing the mucosa with a hemostat or extirpating it with the knife. Ten tubes of a twenty-four-hour-old culture of streptococcus were given daily by the stomach tube at a time when the stomach was empty. This was done in five healthy dogs with negative results, the laceration healing in from six to ten days and the extirpations in from twelve to fifteen days. In other words, Wilkensky and Geist's[22] observations were confirmed. The work was about to be given up when a sixth dog developed distemper after the operation and had recovered three weeks later. The dog was killed and a necropsy was made six weeks after the operation. A large hyperemic, edematous, inflamed ulcer (three-quarters of an inch in diameter) was found at the point of laceration. This dog had been fed *Streptococcus viridans,* which Dr. Clawston isolated from the deep tissues adjacent to the ulcer. The work was continued on two other distemper dogs and in two cachectic dogs with ligated pancreatic ducts. Six weeks after the production of the acute ulcer a necropsy was done on one of the distemper dogs. It revealed an ulcer with con-

22. Wilkensky, A. O., and Geist, S. H.: J. A. M. A. **66**:1382 (April 29), 1916.

gested and edematous edges with a thickened base. This dog had been fed *Streptococcus hemolyticus* which was isolated from the deep tissues about the edges of the ulcer by Rosenow's technic.[23] The second distemper dog which recovered from the distemper four weeks after the operation was killed four weeks later, or eight weeks after the production of the abrasion of the mucosa, and a healing ulcer (Fig. 1)

Fig. 1.—Chronic ulcer (eight weeks) of the pyloric portion of the stomach produced experimentally.

Fig. 2.—Chronic ulcer (ten weeks) of the duodenum produced experimentally.

was found at the site of the abrasion. The edges were congested, edematous and markedly indurated. The cachectic ligated pancreatic duct dog showed at the site of the duodenal abrasion, which was made in this dog, an indurated ulcer with edematous edges (Fig. 2) ten weeks after the production of the lesion. This dog continued to get more emaciated and weaker until it was killed.

23. Rosenow. Jour. Infect. Dis. **17**:219, 1915.

The gastric juice and stomach contents of these dogs were examined at intervals for free acid. Free acid was not found at any time during the attack of distemper or during marked cachexia. This fact is well known to anyone who has worked with Pavlov pouch dogs sick with distemper or showing a disturbance of nutrition.

This study is being continued by a new method that will be more subject to experimental control.

DISCUSSION

The chronic ulcers produced in this study suggest that two other factors are necessary other than an abrasion with a trophic disturbance, infection via mouth or blood stream and acidity, namely, (1) a general lowered resistance, and (2) a temporary hypoacidity or achylia. The animals in which it was possible to delay healing of the acute lesion and to cause it to assume signs of chronicity by feeding streptococci were diseased and cachectic, and showed no free acid in their gastric

Fig. 3.—Ulcer found by Dr. A. B. Luckhardt one inch from a gastrostomy opening in an emaciated dog with both splanchnics sectioned.

juice or contents. It is to be recalled that it was observed in the first study on the occurrence of gastric and duodenal lesions that erosions are much more frequent in the experimental, diseased and cachectic animals. It is well known that diseased and cachectic animals show gastric juice that is deficient in free acidity and often entirely absent. This, of course, makes it possible for any bacteria swallowed or administered to become implanted in the abrasion or local area of hemorrhage or erosion, if present—free acid to the extent that occurs normally in the stomach being incompatible with life for most bacteria. Further, it should be pointed out that an infected lesion in a pathologic mucous membrane—for the mucosa of the stomach is pathologic when it is not secreting its normal gastric juice—is more likely to assume signs of chronicity and to become chronic than a lesion in a normal mucous membrane functioning normally. Therefore, given an abrasion of a pathologic gastric mucosa, a general lowered resistance by disease or disturbed nutrition accompanied by a hypoacidity, we have factors that

make it possible for bacteria swallowed or in the blood stream to become implanted in the abrasion and to produce local inflammation, induration, congestion and edema, and a chronic ulcer. Further, it is reasonable to believe, as observed and pointed out in one animal, that after the edges and base of the abrasion have become infected, inflamed and finally indurated—normal blood supply being diminished thereby—the general condition of the patient may improve or become normal, and yet have the ulcer remain chronic—because of the local diminution of blood supply and edema—and even to become more extensive because of mechanical irritation of coarse foods and tonic gastric activity associated with the action of acid pepsin on the devitalized tissue in the base and about the edges of the ulcer; or even a reinfection may occur during a period of hyposecretion following some digestive disturbance.

It is interesting to recall that acidity is generally considered the all-important factor in the chronicity of the ulcer, which is hardly tenable in light of my observations or those of Rosenow.[16] I recognize, however, that the chronic ulcer that I report might be considered by some to be different from the ordinary peptic ulcer seen clinically. My ulcers may be similar to those found in some cases of achylia gastrica, which some clinicians believe to have a different etiology than peptic ulcer, i. e., trophic.

These results explain the reports of many investigators who have ascribed some other cause to the delayed healing or chronicity. The results of Durante,[7] who produced ulcers chronic in character by section of the splanchnics, are in accord with this conception when the petechial hemorrhages, erosions, temporary hypoacidity and disturbed digestion and loss of weight, that often results along with the temporary lowered resistance from this operation, are taken into account. Durante reports that his animals lived only a short time, which supports my contention. Our double vagotomized and splanchnectomized dogs at this laboratory live indefinitely, but their feeding has to be carefully attended to for the first week or two—in a good state of health, which explains, I believe, why we found no ulcers in our series. Durante's ulcers were infected, as was shown by Rosenow. This conception is also in accord with the findings of Bolton[14] and Friedman and Hamburger,[15] who report that partial pyloric stenosis delays the healing of ulcer. The former investigator suggests that bacterial invasion may have been the cause. Both investigators report that such animals with partial pyloric stenosis vomit, lose weight and become cachectic. This also occurred in some of my dogs. Bolton reports that in some of his animals the gastric contents were neutral or alkaline, but Friedman and Hamburger state that "hyperacidity" resulted in

their animals. The effect of pyloric stenosis upon gastric secretion has not been thoroughly worked out, so this point cannot be settled. Turck's[1] results are in agreement with this conception. Turck produced ulcers by feeding *B. coli* in large amounts over long periods of time to animals that were confined and that manifested abnormal "systemic conditions" with "modified conditions of the alimentary tract." I was surprised to find that this conception is not contrary to Rosenow's observations. In looking over his protocols,[16] I find that the animals that showed chronic ulcers in his series had distemper or some general malaise as shown by anorexia and loss of weight. I do not accept the results of Rosenow as he interprets them with respect to chronic ulcer. Even if his specificity idea is accepted, that does not prove without question of a doubt, that this specific infection is the cause of the chronicity of the ulcer. A mycotic embolus is one of the factors causing acute gastric lesions, or the bacteria may infect an acute lesion otherwise produced. But it is agreed by most workers that acute ulcer in healthy animals heal rapidly no matter how produced. So it is very probable in the light of the results of other investigators and of the results obtained in this study that chronic gastric ulcer has its origin in an acute lesion of the mucous membrane which is infected by swallowed bacteria, or by bacteria from the blood stream, during a time at which the mucous membrane is pathologic—secreting none or but little free acid—and the general resistance is lowered by disease or disturbance of nutrition.

3. METHOD FOR MAKING A PYLORIC POUCH TO BE USED IN THE STUDY OF GASTRIC ULCER

Although several investigators have reported that they were able to produce ulcers of the chronic type, no one has seen a chronic gastric ulcer in the process of development. The method generally employed has been to produce an ulcer in the stomach by some means and then kill the animal some time later and ascertain the condition of the ulcer. Such a procedure is very unsatisfactory experimentally because of the presence of numerous uncontrollable factors. Hardt[24] and Dragstedt[25] approached nearer to the ideal experimental procedure wher they studied ulcer in the Pawlow pouch. But in the Pawlow pouch one is working with a part of the stomach that seldom has ulcer, that heals rapidly, and that produces an acid secretion. The mucous membrane of the pyloric portion of the stomach, on the other hand, is the frequent site of ulcer, heals slower than the fundic mucous membrane

24. Hardt, L. L. J.: Am. J. Physiol. **40**:314 (April) 1916.
25. Dragstedt, L. R.: J. A. M. A. **68**:330 (Feb. 3) 1917.

and does not produce an acid secretion but a mucous secretion slightly alkaline in reaction. So it seems that the ideal experimental procedure, in which all factors might be controlled and chronic ulcer most likely to be produced under daily observation, would be to study the factors (acid, alkalies, irritation, motility, infection, with specific and non-specific bacteria, emaciation, etc.) that influence healing, positively or negatively, in a pouch of the pyloric portion of the stomach.

Hence the operative technic for making such a pyloric pouch has been worked out.

METHOD

Two methods are presented, one for making a pouch with nerves intact, the other for making a pouch with extrinsic nerve supply severed.

With Nerve Supply of the Pouch Intact.—Approximately at a point on the anterior wall of the stomach where the fundic mucous membrane merges into the pyloric mucous membrane an incision one inch long is made through the wall into the lumen of the stomach (Fig. 4, *a*). Through this incision the mucosa is everted and the original incision (a) is continued around the stomach (b), cutting only the mucosa without cutting deeper than the submucosa (as in the Pawlow operation), thus dividing the mucosa into fundic and pyloric portions. The anterior and posterior edges of the fundic mucosa is then sewn together (Fig. 5, c) with a continuous Lembert suture, as is also the anterior and posterior edges of the pyloric mucosa (d), thus forming a wall of the two mucous membranes, which divides the stomach into two compartments, the fundic and pyloric. The incision in the wall of the stomach (a) is then closed by a continuous suture. Next a posterior gastro-duodenostomy (e) is done connecting the fundic compartment with the duodenum. Then a pylorectomy (Fig. 6, f) is done and the pyloric compartment is opened to the outside by a stab wound (g), the pyloric portion of the stomach being anchored to the abdominal wall by a series of interrupted sutures.

With Extrinsic Nerve Supply Severed.—The pyloric portion of the stomach is separated from the rest of the stomach and from the duodenum by incisions "A" and "B" (Fig. 7), care being taken not to interfere with the blood supply of the pyloric portion, which is to be the pouch. An end to side anastomosis (Fig. 8, a′) of the stomach to the duodenum is done and the cut end of the duodenum is closed (b′). Then the opening at the pyloric orifice (b) is closed. Next a large stab wound is made in the abdominal wall and the pouch is anchored in place. The reversal of the pouch so that "a" is brought to the outside instead of "b" makes a larger rosette and the mucosa of the pouch more accessible.

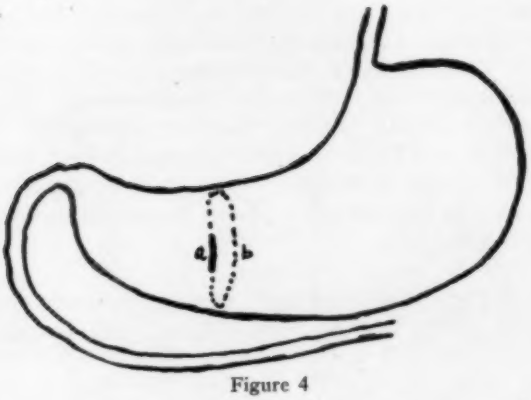

Figure 4

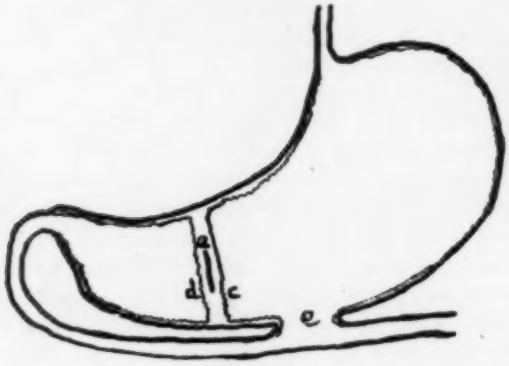

Figure 5

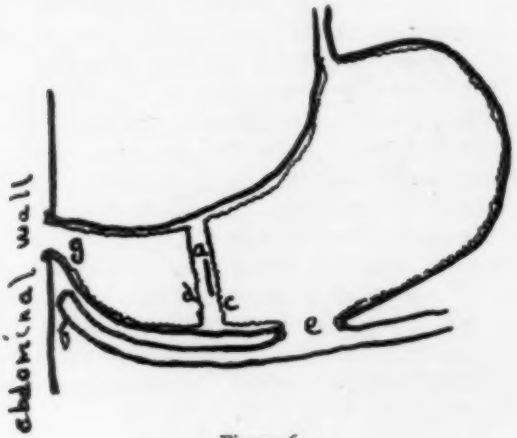

Figure 6

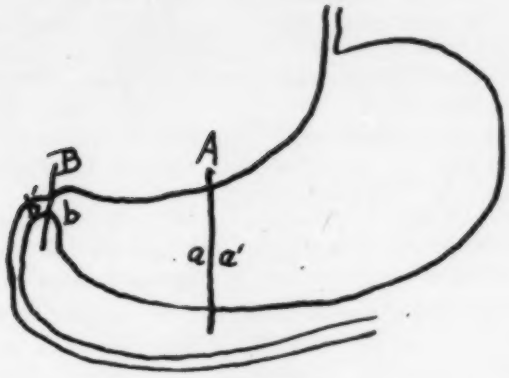

Figure 7

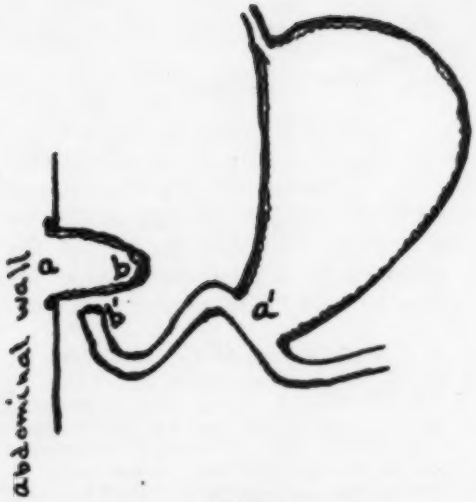

Figure 8

RESULTS

Dogs operated on as described by these methods live indefinitely in a good state of health. Their feeding must be looked after carefully for the first week or two. Bones should not be fed until two or three months after the operation. They cause obstruction at the point of gastroduodenostomy.

The study of the experimental production of chronic ulcer and the factors influencing the healing of acute ulcers is being continued by this method.

4. THE RELATION OF THE LOCATION OF THE ULCER TO CHANGES IN MOTILITY AND EMPTYING TIME OF THE STOMACH

All clinicians are generally agreed that in duodenal ulcer there is a retention of gastric contents and a hyperperistalsis of the stomach. The literature, however, is somewhat at variance concerning the motility of the stomach in ulcers of the pyloric portion of the stomach, unless a stenosis has been produced when the effects upon motility are practically identical with those of a duodenal ulcer. Dundon[26] studied the motility of the empty stomach in the condition of ulcer of the pyloric portion of the stomach and the duodenum. He concluded from his work that the motility of the empty stomach was greater in the condition of ulcer of the stomach and duodenum.

Desiring more complete and definite data on the relation of the location of the ulcer upon changes in motility and emptying time this study was undertaken.

METHODS

The motility of the empty stomach was studied three to five weeks previous to the making of an acute ulcer. The criteria used were: (1) the height of the contraction, (2) the frequency, (3) the length of the hunger and rest periods, (4) the type of the contractions, and (5) the postural and tonic activity of the stomach, the latter being determined by measuring the required amount of air necessary to be put into the balloon to raise the manometer level one inch.[27] This

26. Dundon, J. R.: Am. J. Physiol. 44:234 (Sept.) 1917.

27. The amount of air required is practically constant from day to day, never varying more than 5 c.c. There is quite a variation between different dogs, varying from 15 to 40 c.c. After section of the vagi the amount required is from 10 to 20 c.c. more than normal. This is only temporary; after from ten to twelve days the amount required becomes normal again. It is a question whether this is a true measure of the postural or tonic activity of the stomach. It points in that direction, however. The normal amount required is not influenced by ulcer of the stomach or duodenum. For a day or two after making the ulcer the amount required may be from 5 to 10 c.c. below normal, however.

method of putting a fixed amount of air in the balloon gave a constant base line from which one could comparatively judge more accurately the character of the motility. The size of the balloon, the time of starvation, and as far as possible, the diet were controlled. Bones were not allowed to be fed because they are sometimes found in the stomach twenty-four hours after feeding. The state of nutrition of the dogs was guarded carefully. Dogs with the mange, sniffles, or any other disease were discarded. Ulcers were made by injecting 1.5 c.c. of a 5 per cent. silver nitrate solution beneath the mucosa. Ulcers were made in the anterior wall of the fundus in three dogs, in the anterior wall near the lesser curvature of the pyloric portion of the stomach from one-half to one inch proximal to the sphincter in five dogs and in the first inch of the duodenum in six dogs. Observations were made on the motility of the empty stomach for from three to seven weeks following the making of the ulcer.

Observations were also made on the emptying time of the stomach in ulcer of the fundic and pyloric portions of the stomach and the duodenum. A meal of 100 gm. of ground meat mixed with 50 c.c. of water was fed and its emptying time determined either by gastric fistula, emesis (morphin), and in some cases roentgenographically.

RESULTS

Ulcer of the fundic portion of the stomach had no effect on the motility of the empty stomach, save a slight temporary inhibition for the first two or three days following the making of the ulcer. The same held true for the emptying time, no delay occurring. Healed ulcers were found at necropsy.

TABLE 3.—MOTILITY OF THE STOMACH BEFORE AND AFTER ULCER OF THE DUODENUM; TWENTY-FOUR HOURS' STARVATION

Dog		Average Height of Contraction	Type	Average Length of Hunger Period	Average Length of Rest Period
IX	Before	5 cm.	I	40 min.	1½ hrs.
	After	7 cm.	I, II, III	2 hrs.	1 hr.
XII*	Before	Had to starve 80 hrs. before contractions occurred			
	After	5.5 cm.	I, II	30 min.	1 hr.
XVI	Before	7 cm.	I, II	1¼ hrs.	1½ hrs.
	After	9 cm.	I, II, III	3 hrs.	30 min.
XXI	Before	4.5 cm.	I	1¼ hrs.	2 hrs.
	After	9.5 cm.	I, II, III	2¼ hrs.	1⅝ hrs.
XXXII	Before	5 cm.	I	50 min.	2¼ hrs.
	After	5 cm.	I, II, III	3 hrs.	1½ hrs.
XXXIII	Before	5 cm.	I	1 hr.	3 hrs.
	After	7 cm.	I, II, III	3 hrs.	1 hr.

* An old animal.

Ulcer of the pyloric portion of the stomach caused in three out of five dogs an increase in the motility of the empty stomach. Here, too, a temporary inhibition of the motility for two or three days following the making of the ulcer occurred. The emptying time of the stomach was only interfered with in one of the dogs, in which there was a delay of two hours. In this dog at necropsy an extensive scar was found extending to the pyloric sphincter, but not involving it.

TABLE 4.—SHOWING EMPTYING TIME OF THE STOMACH BEFORE AND AFTER ULCER OF THE DUODENUM

Dog	Normal Time of Emptying	Emptying Time after Ulcer, Duo.	Time Delayed	Remarks
IX	3 hrs.	5½ hrs.	2½ hrs.	
XII	3½ hrs.	5 hrs.	1½ hrs.	
XVI	3 hrs.	5¼ hrs.	2¼ hrs.	
XXI	2¾ hrs.	5½ hrs.	2¾ hrs.	
XXXII	4 hrs.	9 hrs.	5 hrs.	On a full meal this dog often had food in the stomach 24 hours after feeding
XXXIII	3¼ hrs.	5 hrs.	1¾ hrs.	

Ulcer located in the first inch of the duodenum caused an increase in the motility of the empty stomach in all of the six dogs (Table 3, Figs. 9, 10, 11 and 12). This increase was very marked in three of them. A delayed emptying time was observed (Table 4) in every animal. One animal showed a high grade retention to the degree that frequently food, that is on a full meal, was present in the stomach twenty-four hours after feeding. The hypermotility and retention only lasted from two to four weeks. On all these animals a necropsy was done and scars were found.

DISCUSSION

These results show that the clinical symptoms of chronic ulcer with respect to disturbed motility and emptying time of the stomach can practically be duplicated experimentally by an acute ulcer. The inhibition occurring for two or three days after making the ulcer is explained by the observations of Luckhardt[28] to the effect that gastritis inhibits motility, for a temporary gastritis is produced about the area of the injection of the silver nitrate. Why ulcer of the pyloric portion of the stomach and duodenum should disturb motility and ulcer of the fundic portion of the stomach is a question yet to be answered.

28. Luckhardt: loc. cit. Carlson, The Control of Hunger in Health and Disease, Chicago, 1916.

Fig. 9.—Contractions from an old dog (Dog 12, Tables 3 and 4) which had to be starved seventy-two hours before contractions occurred.

Fig. 10.—Contractions from the same dog after forty-eight hours' starvation following a duodenal ulcer.

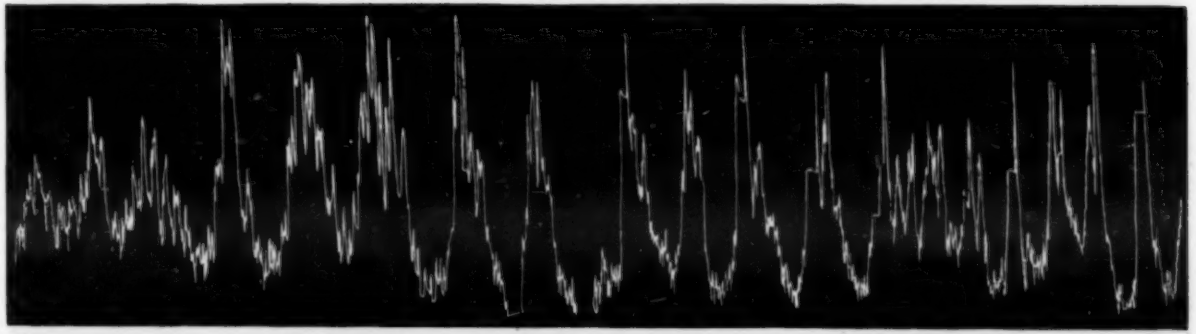

Fig. 11. — Contractions from Dog 9 (Tables 3 and 4) before making the duodenal ulcer,

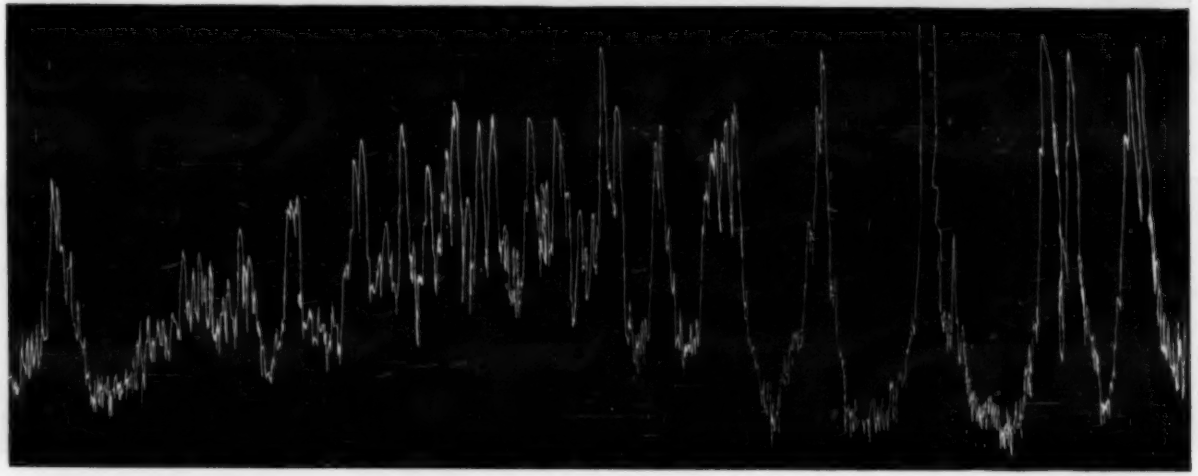

Fig. 12. — Contractions from same dog after making the duodenal ulcer. Dog was starved twenty-four hours in both cases.

5. IS HYPERMOTILITY AND DELAYED EMPTYING OF THE STOMACH IN DUODENAL ULCER DUE TO AN INTRINSIC OR EXTRINSIC MECHANISM?

Hypermotility and delayed emptying of the stomach as a result of duodenal ulcer may be caused by either one or a combination of four mechanisms: (1) to a long reflex to the cord and medulla, (2) to a short reflex to the celiac ganglion, (3) to a local intrinsic reflex, (4) or to an altered metabolic rate. Carlson[29] and Cannon[30] have shown that the isolated empty or full stomach, that is, with the extrinsic nerves sectioned, manifests normal movements. The movements of the isolated empty stomach are chiefly Type I, Types II and III, contractions seldom appearing. Brunemeier and Carlson[31] found that inhibition of contractions by acids, alkalies, water, milk, etc., occur in the isolated stomach, showing that it was possible to inhibit movements of the stomach via local or short nerve paths. Hicks and Vischer[32] showed that duodenal regurgitation when acid was in the stomach and that the characteristic movements by which this was accomplished occurred in the isolated stomach and duodenum. But the literature presents no evidence as to whether augmentation, or increased motility, can be brought about by local reflexes. On the other hand, the literature draws our attention to the importance of the extrinsic mechanism and uses the vagus nerve to explain all conditions of hypermotility, retention, pylorospasms, etc., without considering the possible importance of an intrinsic mechanism.

METHODS

Both vagi and splanchnics were sectioned and the celiac plexus was extirpated. Records were made of the motility of the empty stomach, using the criteria mentioned in Study 3. An acute ulcer was made in the first inch of the duodenum and changes in motility were observed.

Observations were made on the emptying time of the stomach before and after the ulcer. A meal of 100 gm. of ground meat mixed with 50 c.c. of water was fed.

RESULTS

An increase in the motility of the isolated empty stomach occurred (Table 5) following the making of the acute ulcer in the duodenum (Figs. 13, 14, 15 and 16). The degree of increase was not as great as that noticed when the extrinsic nerves were intact (Table 3). All

29. Carlson, A. J.: Am. J. Physiol. **32**:369, 1913.
30. Cannon, W. B.: Am. J. Physiol. **36**:191, 1915.
31. Brunemeier and Carlson: Am. J. Physiol. **36**:191, 1915.
32. Hicks and Vischer: Am. J. Physiol. **39**:1, 1915.

TABLE 5.—Motility of the Stomach Before and After Ulcer of the Duodenum in Dogs with Both Vagi and Splanchnics Sectioned and Celiac Plexus Extirpated, Twenty-Four Hours' Starvation

Dog		Average Height of Contraction	Type	Average Length of Hunger Period	Average Length of Rest Period
I	Before	6 cm.	I	1 hr. 40 min.	2 hrs.
	After	9 cm.	I	3 hrs. 20 min.	2 hrs.
I-A	Before	4 cm.	I	1 hr.	1 hr.
	After	8 cm.	I	2 hrs.	45 min.
XXXIII	Before	Contraction negligible on 24 hrs. starvation			
	After	8 cm.	I	3 hrs.	30 min.
XXI	Before	5 cm.	I	30 min.	1½ hrs.
	After	7 cm.	I	3½ hrs.	20 min.

Fig. 13.—Contractions from Dog 33 (Tables 5 and 6) with both vagi and splanchnic sectioned and celiac plexus extirpated and starved twenty-four hours. Note type of contractions in the isolated stomach.

TABLE 6.—Showing Emptying Time of the Stomach Before and After Ulcer of the Duodenum in Dogs with Both Vagi and Splanchnics Sectioned and Celiac Plexus Extirpated

Dog	Normal Time of Emptying of Isolated Stomach	Emptying Time after Ulcer of Duodenum	Time Delayed
I-A	3¼ hrs.	4¾ hrs.	1½ hrs.
XXXIII	3¾ hrs.	5 hrs.	2¾ hrs.
XXI	3 hrs.	5 hrs.	2 hrs.

Fig. 14.—Contractions from the same dog after twenty-four hours' starvation with duodenal ulcer.

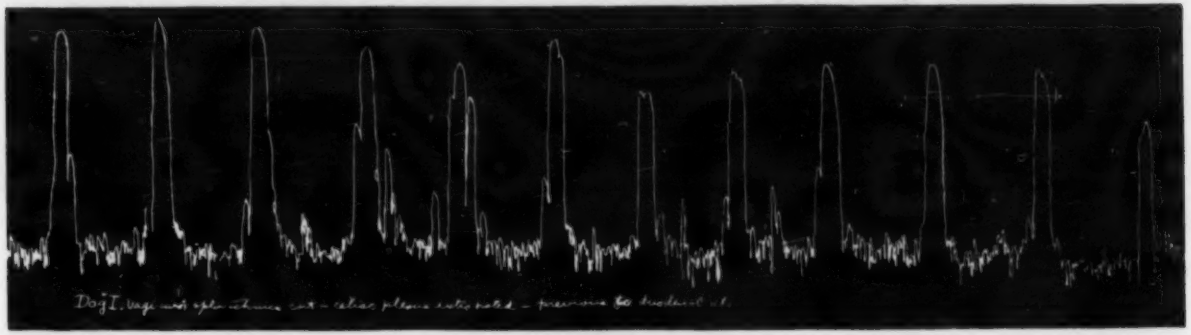

Fig. 15.—Contractions from Dog 1 (Tables 5 and 6) with both vagi and splanchnics sectioned and celiac plexus extirpated and starved twenty-four hours.

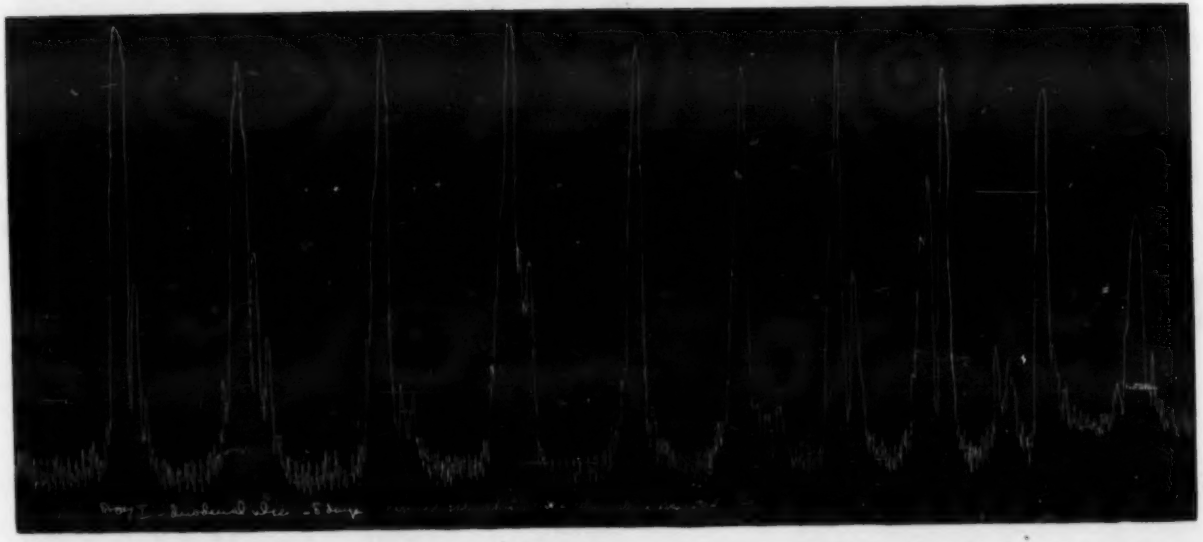

Fig. 16.—Contractions from the same dog after twenty-four hours' starvation with duodenal ulcer.

contractions were Type I, showing that the prevalence of Types II and III in normal animals (Table 3) with duodenal ulcer was due to an extrinsic mechanism.

The emptying of the stomach was delayed (Table 6), not so much as when the extrinsic nerves were intact (Table 4).

During the course of this study Brunemeier and Carlson's[31] observations on the inhibitory effect of alkalies and acids on the motility of the isolated stomach was repeated and confirmed.

DISCUSSION

These results show that the fundamental cause of the gastric hypermotility and delayed emptying of the stomach in duodenal ulcer is intrinsic, and that it is enhanced by the presence of the extrinsic nervous mechanism, the rôle of the latter being to increase the frequency of the contractions occuring on gastric tone, or Types II and III.

Although these results show that hypermotility and delayed emptying of the stomach in duodenal ulcer are due to intrinsic mechanism, they do not teach us the nature of the mechanism. There are two possibilities: (1) an increased irritability of the intrinsic nervous reflex, and (2) an altered metabolic rate.

ADDENDUM

Since writing this article my attention has been called to an article by Carman[33] in which he differentiates between extrinsic and intrinsic spasm by the use of atropin. He states that "intrinsic spasm plays an important part in the roentgenologic evidence of duodenal ulcers, and that in the absence of spasm no deformity of the bulb would be seen in many instances, and the case passed as negative." It is very interesting and important to note that my experimental results corroborate this clinical finding.

33. Carman, R. D.: J. A. M. A. **66**:1283 (April 22) 1916.

THE EFFECT OF ROENTGEN RAYS ON THE METABOLISM OF CANCER PATIENTS*

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The ever increasing scope of blood chemistry studies has enabled us to estimate quantitatively factors representing protein, fat, carbohydrate and salt metabolism and storage.

Everyone is familiar with the cachexia of cancer sufferers, and the early stage at which it sometimes appears, making it practically a diagnostic symptom of malignancy. With this in mind, our efforts have been directed toward the actual cause of the loss of weight, whether due to (1) deficient food intake; (2) absorption of toxins from secondary infection of the tumor, or (3) to some specific action of cancer cells that prevents storage and utilization of foodstuffs.

Following radium and roentgen-ray treatments, many patients show marked improvement or are cured, and the question arises as to whether the roentgen ray produces any discernible change in the blood chemistry and how long such a change must exist to affect a general improved metabolism, and whether the effect of the roentgen ray is a general one or only a local destructive action on tumor cells.

We, therefore, chose ten readily estimable factors for the study of the blood chemistry, and the complete studies were made immediately before roentgen ray exposure, one half an hour after, and on the next day, approximately twenty-four hours afterward. The entire study is preliminary to, and in the nature of a report of the broader observations with which we are now engaged. The following were estimated in mg. per 100 c.c. of blood in each instance: 1. Urea. 2. Creatinin. 3. Uric acid. 4. Chlorids. 5. Cholesterol. 6. Fatty acids. 7. Total fats. 8. Sugar. 9. Diastatic activity. 10. Plasma and corpuscle percentage. The cases selected for study were not taken at random as only those patients were selected who were practically free from renal disease, in order to obviate the matter of retentions. Several control studies were made on normal people subjected to the same roentgen-ray exposure. With another control group of cancer patients, we took 60 c.c. of blood at the same interval as in the roentgen-ray studies but without roentgen-ray exposure.

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UREA

The urea content of the blood has been much studied as to its source and utilization. It bears a close relation to the amino acids and its production probably depends on the activity of all the living

TABLE 1.—UREA NITROGEN CONTENT OF BLOOD
Mg. per 100 c.c.

Number	Before Roentgen-Ray Exposure Per Cent.	One-Half Hour After Roentgen-Ray Exposure Per Cent.	Twenty-Four Hours After Roentgen-Ray Exposure Per Cent.
1	5.6	14.0	8.4
2	12.0	21.0	12.6
3	9.8	14.0	14.0
4	5.6	7.0	14.0
5	16.8	19.6	15.4
6	14.0	7.0	8.4
7	12.6	14.0	8.4
8	7.0	4.2	2.8
9	11.8	14.0	16.8
10	8.4	13.6	33.6
11	11.8	12.6	9.8
12	15.4	16.8	14.0
13	9.8	12.6	8.4
14	9.8	8.4	9.8
15	9.8	14.0	12.6
16	12.6	15.4	14.0
17	11.2	14.0	23.8
18	9.8	25.2	11.2
19	9.8	12.6	12.6
20	23.8	15.4	16.8
21	11.2	23.8	18.6
22	5.6	8.4	5.6
23	14.0	14.0	14.0
24	11.2	11.2	7.0
25	11.2	8.4	8.18
26	19.7	21.0	11.2
27	14.0	12.6	22.4
28	16.8	23.8	18.2
29	11.2	15.4	21.0
30	5.6	9.8	5.6
31	12.6	17.8	19.6
32	8.4	11.2	25.2
33	12.6	14.0	11.2
34	5.6	23.8	21.0
35	11.8	26.6	9.8
36	9.06	15.4	21.0
37	12.0	18.0	....
38	16.8	18.2	....
39	29.5	28.0	....
40	8.4	9.8	....
41	9.8	14.0	....

cells rather than of any fixed group. With renal injury, either slight or severe, urea is so consistently retained and piled up in the blood stream that a definite prognosis can be given such a case on the

amount of urea present. It is an excellent kidney function index, and can be used practically alone as such, if the protein intake is known. McLean and Mosenthal have worked out the index of urea excretion with precision and added much to our knowledge of its value in the prognosis and treatment of various renal diseases.

Its relation, however, if it has any special one, to malignancy has not yet been recorded, and the few observations we make at this time are entirely preliminary to our more complete studies of urea and the amino acids in relation to cancer. There is some question as to whether the rapidly growing tumor cells have a special activity as regards urea and amino acid chemistry, apparent early in the precancerous condition and which would thereby aid in diagnosis and treatment at an earlier stage. Of the forty-one cases studied, eleven patients were improving, seven had had tumors removed and were improving, twelve were progressing and six were clinically well. Thirty-one cases showed increased urea, one half hour after roentgen-ray exposure, and of these, twenty still showed increased urea on the day following. Of the seven cases with urea decreased one-half hour after roentgen-ray exposure, five were progressive with no improvement, one was a healthy person and one had an improving epithelioma of the nose.

It can, therefore, be seen that there is nothing characteristic about the conduct of urea formation that would aid in early diagnosis without the simultaneous amino acid and protein intake studies. The increase in urea was at no time exceedingly high. It was only a relative increase. The reduction of body proteins into amino acids, and urea formation therefrom could account for the slight increases, and it is quite possible that the tumor cells, exposed to the roentgen rays, themselves furnish enough amino acids to account for the increase in urea in some of the cases. The increase one-half hour afterward in some cases, and not until the day following in others, can be accounted for partly by the variation of response of living tissue to the same stimulus. It is possible that the conversion of proteins to amino acids is accelerated in these exposed cases by ferments activated by the rays, in which case the exposure of any part of the body other than the tumor would have the same effect on the urea chemistry. As there is still some indecision as to whether there is actually the same result with diffuse exposure to roentgen rays we cannot at present make a definite statement. The urea determinations were made by the urease, areation and titration method with control checks to insure their accuracy.

CREATIN AND CREATININ

The study of the metabolism of creatin and creatinin in malignancy has been very limited, and it has only been in recent years that the definite relationship between the two has been made clear. Methods

TABLE 2.—CREATININ CONTENT OF BLOOD
Mg. per 100 c.c.

Number	Before Roentgen-Ray Exposure Per Cent.	One-Half Hour After Roentgen-Ray Exposure Per Cent.	Twenty-Four Hours After Roentgen-Ray Exposure Per Cent.
1	0.66	0.571	0.09
2	0.26	0.63	0.5
3	0.8	0.62	0.7
4	0.83	0.67	....
5	0.71	0.68	....
6	0.43	0.58	0.5
7	0.52	0.55	0.35
8	0.58	0.39	0.45
9	....	.....	....
10	0.8	0.56	0.13
11	1.0	0.91	0.72
12	0.73	0.85	1.37
13	0.8	1.1	0.57
14	1.1	0.76	0.71
15	0.89	0.99	0.5
16	0.99	0.8	1.05
17	0.4	0.4	0.4
18	....	.....	....
19	0.714	0.714	1.01
20	0.83	1.142	1.25
21	0.909	2.22	0.5
22	0.909	0.52	0.26
23	0.8	1.25	0.71
24	0.909	0.909	0.606
25	0.9	0.44	0.54
26	0.59	0.67	0.72
27	....	.....	....
28	0.5	0.5	0.53
29	1.05	0.571	0.09
30	0.63	0.53	0.5
31	0.87	0.5	0.83
32	1.0	1.1	0.8
33	0.95	0.85	0.9
34	0.83	0.84	0.87
35	0.83	0.83	0.83
36	1.81	1.33	1.1
37	0.66	0.71	....
38	1.2	1.2	....
39	....	.....	....
40	0.81	0.85	....
41	0.57	0.88	....

for the determination of these factors in the blood can still be improved. In our work we used acetic acid precipitation of the blood and picric acid precipitation with parallel results but rather low readings. Although in all instances it was possible to recover

creatinin which we added to the blood, we are not satisfied that we have completely extracted the creatinin already present in the blood. Meyer and Fine[1] have shown that creatin is slowly changed to creatinin even in pure solution, and much more rapidly in autolyzing muscle tissue. The increased creatinin in the blood in nephritis is due most probably to a retention rather than to an endogenous increase as it becomes much higher in the blood than in the muscle tissue itself, and there is practically no alteration in the creatinin content of either. Marcelle Wahl[2] studied creatin in the urine of a variety of diseases, and among them some cases of cancer. In cancer with no metastasis in the liver he found barely a trace of creatin, but, on the contrary, in cases of cancer with liver metastases the elimination of creatin was definitely high.

R. A. Chisholm[3] reported a study of creatinin content of muscle in malignancy, but although there is a great deal of literature on the relation of creatin and creatinin to muscle activity, starvation, pregnancy, nephritis, etc., further studies have been much lacking in regard to this factor and its relation to cancer.

Fifteen of our cases had an increased amount of creatinin in the blood one-half hour after roentgen-ray exposure; in twenty cases it decreased the day after, and in eight it was still increased on the day following when three cases showed no change in the amount of creatinin and eighteen cases were decreased one-half an hour after roentgen-ray exposure. There were no renal cases and no creatinin content greater than would be expected in the normal person.

We can find nothing characteristic of cancer in the variation of the creatinin content of the blood, and apparently there is no alteration of creatinin metabolism in this disease.

URIC ACID

Uric acid was discovered in urinary calculi in 1776 by Schule, and in gouty tophi by Wallaston in 1797. In 1882, Salkowski introduced a method for the quantitative estimation of uric acid, and altogether, during the past century and a half, an enormous amount of research has been done on this subject not only on humans, but on the lower animals, including birds.

About 1899, Emil Fischer classified uric acid as a definite chemical entity, and showed its relation to the purin nucleus and other bodies as hypoxanthin, xanthin, adenin, and guanin, all of whose structures

1. Myers, V. C., and Fine, M. S.: J. Biol. Chem. **21**:460 (June) 1915.
2. Wahl, Marcelle: Arch. de méd. exper. et d'anat. path. **28**: No. 2.
3. Chisholm, R. A.: Biochem. J. **4**:243, 1911.

depend on slight changes around the purin nucleus. Salmon, in 1880, discovered that purin bases exist in nuclein of cell nuclei, and that the products obtainable from neucleoproteins are varied and numerous.

TABLE 3.—Uric Acid Content of Blood
Mg. per 100 c.c.

Number	Before Roentgen-Ray Exposure Per Cent.	One-Half Hour After Roentgen-Ray Exposure Per Cent.	Twenty-Four Hours After Roentgen-Ray Exposure Per Cent.
1	2.9	4.	4.
2	3.2	2.42	4.1
3	3.75	2.66	3.15
4	3.	2.85	3.
5	1.29	1.26	0.93
6	2.5	2.85	3.92
7	4.4	3.9	4.
8	2.66	3.33	3.8
9	4.46	2.94	1.1
10	3.8	3.6	3.6
11	3.	3.3	4.
12	2.	2.35	1.33
13	1.9	2.85	2.9
14	2.58	1.87	1.75
15	2.	1.14	2.5
16	2.5	2.5	2.6
17	3.63	3.07	3.8
18	1.74	3.125	3.85
19	1.89	1.89	3.63
20	2.17	1.85	1.81
21	2.8	3.	2.5
22	2.2	2.5	1.9
23	1.81	3.3	1.81
24	3.	3.	1.3
25	5.3	4.	4.
26	5.5	6.25	3.57
27	5.5	5.	4.54
28	2.	1.3	4.
29	2.02	2.5	5.5
30	2.85	3.07	5.71
31	2.	2.5	2.5
32	3.33	3.65	3.2
33	1.29	1.93	1.28
34	2.34	3.63	3.63
35	1.81	2.27	3.22
36	1.8	2.7	1.15
37	2.71	0.857	....
38	2.	2.17	....
39	3.28	3.57	....
40	1.8	2.	....
41	2.3	2.1	....

The normal range of uric acid in the human blood is from 0.5 to 1.5 mg. per cent. It is rarely below 0.5 mg. and commonly over 1 mg.

The sources of uric acid in the blood may be divided into: 1. Exogenous or ingested. 2. Endogenous or from body catabolism.

The exogeneous source of uric acid is from foods containing purins and nucleoproteins, such as meat extractives, glandular tissue, peas, beans, etc. The purins ingested as free base or as nucleic acid are at least partially converted into uric acid which is the most highly oxidized member of the purin compounds. We still know very little of catalytic processes of purins in the body. Uric acid in the blood is excreted for the most part and very little is oxidized in the body. Its excretion is increased after ingestion of purins or any food that increases its concentration in the blood. Uric acid is a physiologic diuretic and its excretion depends chiefly on kidney cell activity so that it is being constantly excreted in varying amounts, but always with an effort at maintaining a constant concentration in the blood. If there is any kidney injury, such as occurs with varying degrees of nephritis, the threshold of excretion of uric acid is raised and the "constant concentration" of the uric acid in the blood is much higher than normal and may reach a level of from 6 to 8 mg. per cent. This level may become very high with unrestricted purin diet, but, of course, in a true retention of uric acid there are the other signs and symptoms of renal insufficiency to aid in a diagnosis.

There is the gouty type in which there seems to be a selective retention of uric acid. Purin diet, in these cases, gives a very high blood uric acid which, however, is excreted on the administration of atophan and salicylates, until a normal level is reached. The high uric acid of renal insufficiency does not behave in this way, as medication acts only as an irritant to the already overworked cells and serves to cause a greater retention than before. In an actual nephritis, where the uric acid in the blood comes from both exogenous and endogenous sources, its concentration in the blood can be lowered effectively by restricting all purin foods. We can see what an important part the exogenous source of uric acid plays in keeping up the normal amount of uric acid in the blood. It is easily observed and controlled, and it is quite simple to eliminate this source of a high uricacidemia, in making a study of a case.

Endogenous uric acid has several sources, much more difficult to study than the exogenous variety. We are unable to tell exactly where the endogenous purin precursors of uric acid are; but we can say that the breaking down of body purins, such as the free hypoxanthin of muscle, and the breaking down of nucleoprotein from pus cells as in focal infection or leukocytosis, or from local necrosis in any parenchymatous tissue, form the chief sources of endogenous uric acid. Exercise, of course, increases the uric acid in the blood

and it is well known that uric acid is increased in the leukemias where there are so many leukocytes constantly breaking down and undergoing digestion. Valuable information can be obtained as to the existence of focal infection by studying the uric acid in the blood and eliminating other causes of a high uric acid, such as food, exercise, nephritis, etc. With these ruled out the uric acid must be derived from some focus of infection from which a constant stream of nucleoprotein and purin material is being poured into the blood stream.

The amount of uric acid in the blood depends on the area and degree of absorption from the above mentioned sources. We have seen the high uric acid of several patients drop to normal after the removal of areas of absorption, as in infected tonsils, gangrenous toe, alveolar abscesses, necrotic epitheliomas, etc., absorption from the areas of degenerating material undoubtedly being the cause of the high uric acid content in each case.

With these simple, well known facts in mind, we included the observation of the uric acid in the blood in our roentgen-ray study, believing that a temporary and possibly a permanent change could be produced in an individual exposed to the rays. All cancer cases do not necessarily have a high uric acid content in the blood, especially where the tumor is uninfected. If, however, there has been infection of the mass with central necrosis, the uric acid is increased directly in proportion to the amount of absorption of nucleoprotein material.

Of the thirty-six patients studied, only two had a normal uric acid in the blood before roentgen-ray exposure. In twenty cases the uric acid was increased, one-half hour after roentgen-ray exposure, and in sixteen cases it was lower after than before such exposure. Fourteen of these sixteen cases had an excessively high uric before roentgen-ray treatment. On the day following treatment, twenty patients still had a high uric acid, in fifteen the uric acid was lower than before roentgen-ray exposure and in the remaining case the uric acid was unchanged. Of the fourteen cases in which the uric acid was lower on the day following roentgen-ray exposure, four patients were becoming worse; two were improving; four were operated on with no recurrence; one patient, a control case, was not subjected to roentgen-ray treatment. Of the twenty-two patients having an increased uric acid content the day after roentgen-ray exposure, one was becoming worse; four were improving; two were operated on with no recurrence; three were clinically well; one patient left and has not returned; one patient is a normal roentgen-rayed control. The

three noncancerous control persons were not exposed to the rays quite as long as were the patients. They had a lower uric acid content on the day following roentgen-ray exposure. Four of the patients studied have since died from their cancers, three having a very high uric acid content on the day following roentgen-ray exposure and the other remaining unaltered.

There is no relation between the progress of the patient and the uric acid in the blood. Roentgen rays can be said to increase the uric acid content of the blood only by destruction of tissue or by causing a leukocytosis with subsequent destruction of leukocytes producing a uric acid increase for a short period of time. The effect of the roentgen ray varies in different individuals, some getting a more severe reaction than others, so that the amount of increase of uric acid in the blood depends on the dosage of roentgen rays, the condition of the tumor and the condition of the patient. Here, neither an increase nor a decrease in uric acid is permanent. It may last a few hours or a few days.

Rosenberg, in 1906, observed the uric acid excretion in leukemias and some other diseases. He reported on increased excretion in the leukemias only. No blood studies were made at the time, but there must have been with the increase in urinary excretion a corresponding increase in the uric acid content of the blood.

CHLORIDS

The normal range of chlorids in the blood as sodium chlorid varies from 400 mg. to 650 mg. Five of our patients had a chloridemia of more than 650 mg. before treatment. They had either mouth or laryngeal or esophageal cancers and drank very little water. These same individuals had high corpuscle percentages and none of them were in any marked degree nephritic.

Thirty-five patients had normal blood chlorids before roentgen-ray exposure. One half-hour after roentgen-ray treatment the chlorids were slightly increased in quantity in sixteen cases, decreased in twenty cases and unchanged in four cases. Of these cases, five only were out of normal limits. Twenty-four hours after exposure, fifteen patients still had a higher chlorid content than they had before being rayed, and in twenty patients it was lower.

The total range of chlorid concentration was within normal limits in all but six cases, in five of these it was abnormally high during the whole period of observation, due to the low fluid intake; and in one

case the chlorid content had increased from normal to a hyperchloridemia on the day following treatment.

The sodium chlorid content of the blood of cancer patients is normal, and is unaffected by roentgen rays.

TABLE 4.—CHLORID CONTENT OF THE BLOOD
Mg. per 100 c.c.

Number	Before Roentgen-Ray Exposure Per Cent.	One-Half Hour After Roentgen-Ray Exposure Per Cent.	Twenty-Four Hours After Roentgen-Ray Exposure Per Cent.
1	450.0	475.0	337.5
2	437.5	413.0	450.0
3	525.0	400.0	437.5
4	563.0	400.0	475.0
5	437.5	437.5	425.0
6	412.0	437.5	437.5
7	437.5	437.5	437.5
8	425.0	475.0	487.0
9	425.0	450.0	425.0
10	275.0	437.5	500.0
11	400.0	437.5	423.5
12	463.5	375.0	500.0
13	475.0	463.5	463.5
14	475.0	435.0	437.5
15	463.5	437.5	450.0
16	475.0	435.0	700.0
17	720.0	800.0	600.0
18	712.5	850.0	993.5
19	337.5	428.0	462.5
20	337.8	312.5	487.5
21	462.5	500.0	425.0
22	500.0	600.0	463.0
23	425.0	475.0	512.5
24	525.0	412.0	475.0
25	437.5	437.5	425.0
26	250.0	475.0	550.0
27	375.0	275.0	425.0
28	432.5	412.5	462.5
29	475.0	437.5	462.5
30	450.0	462.5	239.5
31	460.0	425.0	460.0
32	650.0	600.0	620.0
33	700.0	667.0	687.5
34	362.5	562.5	437.5
35	462.5	635.0	463.5
36	563.0	475.0	475.0
37	525.0	400.0	.....
38	703.0	705.0	.....
30	875.0	925.0	.....
40	450.0	435.0	.....
41	375.0	387.5	.....

CHOLESTEROL

Cholesterol was discovered in gallstones by Conradi, in 1775, and named, in 1815, by Chevraul and since that time very little progress has been made until during the last fifteen years, when with newer

and more accurate methods, comparative studies have been possible. Physiologists practically all agree now that cholesterol is ingested with the food, liberated in the intestinal tract, is then esterized and

TABLE 5.—Cholesterol Content of Blood
Mg. per 100 c.c.

Number	Before Roentgen-Ray Exposure Per Cent.	One-Half Hour After Roentgen-Ray Exposure Per Cent.	Twenty-Four Hours After Roentgen-Ray Exposure Per Cent.
1	121.0	115.0	287.0
2	125.0	156.2	130.0
3	233.0	198.0	265.0
4	267.0	198.0	250.0
5	163.0	187.0	375.0
6	175.0	187.5	69.3
7	175.0	178.0	175.0
8	94.0	175.0	109.0
9	120.0	125.0	150.0
10	160.0	234.0	175.0
11	208.0	269.0	250.0
12	187.5	312.5	312.5
13	137.0	189.0	269.0
14	185.0	144.0	125.0
15	178.0	320.0	312.0
16	138.0	125.0	187.0
17	208.3	208.3	208.3
18	179.0	108.7	*
19	107.75	237.3	250.0
20	133.8	84.0	104.0
21	156.2	187.5	178.5
22	208.0	234.0	208.0
23	187.5	226.0	210.6
24	288.0	170.4	208.3
25	175.0	104.0	93.0
26	187.0	133.0	133.0
27	156.0	187.0	133.0
28	98.0	156.2	156.2
29	67.0	156.2	162.5
30	134.0	156.2	187.5
31	180.0	250.0	270.0
32	208.3	250.0	163.0
33	191.3	150.0	144.2
34	173.6	173.6	185.6
35	102.9	183.8	208.3
36	200.0	234.0	234.0
37	187.0	395.0	*
38	175.0	175.0	*
39	208.3	208.3	*
40	150.0	187.5	*
41	208.3	187.5	*

* No estimation made.

absorbed by the lymphatics to be delivered to the blood stream and so distributed to the body cells. This exogenous source of cholesterol is the largest and most important one. Later, as these cells die and become autolyzed, their content of cholesterol is again delivered to

the blood stream, removed by the liver, excreted through the bile and in large part reabsorbed, thus forming the endogenous source of cholesterol, if it may be so called.[4] There is no proof that cholesterol may be synthesized in the body. In the egg it has been shown that there is no gain in cholesterol during the incubation of the chick.[5] The body depots for blood cholesterol are the skin, eye tissues, biliary vesicles and the atheromatous areas of arteries.

Ignatowski, of the Russian school at St. Petersburg, first observed tissue lesions resulting from abnormal foods. He suspected animal proteins to be the cause of the injury. Stuckey[6] showed that egg white and meat juice, fat and lecithin had no effect, but that cholesterol gave uniform results. It caused an increased endothelial activity, the arteries of the lung tissue showing the greatest arterial changes, then those of the kidney, heart and spleen. The suprarenal cortex, liver cells and intima of arteries act as intermediate organs for the final disposal of cholesterol esters.

In man as in animals the excretion of cholesterol in the feces can be accounted for by that taken in with the food when the body weight remains constant. If, however, a rapid loss in weight takes place, the output of cholesterol exceeds the intake.[7] This total and free cholesterol is very constant per kilogram of body weight. On forced cholesterol feeding or in a marked cholesterinemia considerable cholesterol has been found in the suprarenals as well as in the liver. This fact gives rise to the question as to how much the suprarenals have to do with the cholesterin metabolism. The liver and not the adrenals is the chief organ for the control of cholesterin metabolism according to one author.[8] Luden believes that faulty metabolism causing high cholesterol in the blood, is closely associated with cell proliferation. She says that the integrity of the liver function plays an important and probably prominent part in the etiology of malignant disease. She has shown that a patient with a malignant proliferation in the liver gives the highest cholesterol values in the blood.[9]

In this study it was our intention to compare the cholesterol content of the blood of cancerous people with normals, and to ascertain whether roentgen-ray exposure alters this content in any way.

Forty-one cases were studied. Before roentgen-ray treatment, twenty-three patients had a hypercholesterinemia; thirteen were normal. One-half hour after roentgen-ray treatment, twenty-five had

4. Taylor: Digestion and Metabolism, 1912.
5. Doree and Gardner: Proc. Roy. Soc., Lond. **81**: 1909.
6. Klotz, O.: Med. Res., **33**:157 (Nov.) 1915.
7. Ellis, G. W., and Gardner: Proc. Roy. Soc., Lond. **86**:13, 1913.
8. Rothchild, M. A.: Proc. N. Y. Path. Soc. **14**:229, 1914.
9. Stewart, M. J.: J. Path. & Bact. **19**:305, 1914.

reached a higher cholesterol figure than before; in three the cholesterol was unchanged, and in thirteen the cholesterol blood content was lower. Twenty-four hours after roentgen-ray treatment the cholesterol content in twenty cases had reached a higher figure; in six cases a third estimation was not made; in three cases the cholesterol content was unchanged, and in twelve cases it was lower than normal. One-half hour after treatment the cholesterol content was higher in eleven cases, unchanged in six and lower in nineteen cases. In six cases no estimation was made. We are unable to draw any definite conclusions from these results in regard to the size or type of tumor, its location or the duration of the exposure to the rays. On the other hand, one-half hour after roentgen-ray treatment, we find that in 61 per cent. of our series of forty-one cases the cholesterol figures were higher than they were before treatment. In 31 per cent. of the cases the cholesterol content was lower than before treatment. The findings twenty-four hours afterward are not any more conclusive but they are of interest in that they indicate the ability of the organism to handle an excess of cholesterol. Whether this is an index of one of the functions of the liver or simply of a lowered ability of the tissues to combine with the cholesterol, we cannot say. We can say, however, that exposure to roentgen ray in the majority of cases causes an increase in cholesterol content in the blood, although this increase is not proportional to the time of exposure or the type of tumor. It probably is due to the autolysis of the cells by the rays, resulting in the liberation of this substance.

FATTY ACIDS

If we take 500 mg. as the high normal of fatty acids, we find that in thirty-six cases, or 90 per cent., the fatty acid content of the blood is higher than normal before roentgen-ray treatment. One half hour after exposure, an increase in the fatty acids was found in thirty-four cases, or 83 per cent.; a decrease from the first estimation in thirty-five cases, or 61 per cent.; an increase over the first estimation in twelve cases, or 31 per cent., and in three cases, or 8 per cent., the amount of fatty acids was practically unchanged. Twenty-four hours after exposure there was an increase in the fatty acids in the blood in twenty-eight cases, or 80 per cent.; a decrease from the first estimation in twenty-six cases, or 72 per cent., and an increase from the first estimation in six cases, or 16 per cent.

It is evident that this series of cancer cases has a very high percentage of increased fatty acids in the blood, and that this percentage is reduced by roentgen-ray exposure. In most of these cases, the

decrease was noted one-half hour after the exposure, although the percentage of cases showing decreased fatty acids was still larger at the end of twenty-four hours. We can say, therefore, that roentgen-ray exposure oxidizes the fatty acids and that the results of this

TABLE 6.—FATTY ACIDS IN THE BLOOD
Mg. per 100 c.c.

Number	Before Roentgen-Ray Exposure Per Cent.	One-Half Hour After Roentgen-Ray Exposure Per Cent.	Twenty-Four Hours After Roentgen-Ray Exposure Per Cent.
1	788.0	702.0	405.0
2	774.0	677.8	704.0
3	943.0	1340.0	687.0
4	785.0	978.0	659.0
5	746.0	813.0	375.0
6	480.0	479.1	643.9
7	658.2	562.0	565.0
8	798.8	538.2	557.0
9	620.0	481.0	505.0
10	515.0	430.0	400.0
11	1354.0	1397.0	831.0
12	1553.5	739.5	687.5
13	1681.0	2033.0	631.9
14	1114.0	1376.0	927.0
15	998.0	930.0	789.0
16	2084.0	1087.0	527.0
17	947.7	849.7	757.7
18	1000.0	917.0	1149.0
19	1086.0	909.0	909.0
20	1438.0	1117.0	966.0
21	1271.8	1351.5	1271.5
22	968.0	675.0	792.0
23	1351.5	683.0	789.4
24	823.0	940.6	591.7
25	459.0	784.8	713.4
26	436.0	481.0	533.0
27	533.0	479.0	527.0
28	795.0	612.8	647.8
29	706.0	612.8	912.5
30	735.0	584.8	479.5
31	772.0	720.0	668.0
32	940.7	879.0	1020.0
33	774.7	788.0	780.0
34	1116.4	527.4	743.4
35	846.1	566.2	591.7
36	436.0	345.0	442.0
37	722.0	909.0	*
38	*	*	*
39	687.7	604.7	*
40	683.0	1293.5	*
41	606.7	923.5	*

* No estimation.

last at least twenty-four hours. Further than this we do not care to express ourselves at present. At a future date we hope to have a more complete series of fat studies and to be able to draw a more definite conclusion.

TOTAL FATS

The digested fat of the diet is split into glycerol and fatty acids, which recombine in the cells of the intestinal mucosa into the original fat. The greater part of the fat is then collected in the lacteals and

TABLE 7.—TOTAL FATS IN THE BLOOD
Mg. per 100 c.c. of blood

Number	Before Roentgen-Ray Exposure Per Cent.	One-Half Hour After Roentgen-Ray Exposure Per Cent.	Twenty-Four Hours After Roentgen-Ray Exposure Per Cent.
1	909.0	817.0	692.0
2	909.0	834.0	834.0
3	1176.0	1538.0	952.0
4	1052.0	1176.0	909.0
5	909.0	1000.0	754.0
6	655.0	666.6	713.2
7	833.3	740.0	740.0
8	892.8	713.2	666.0
9	714.0	606.0	655.0
10	657.0	664.0	606.0
11	1562.0	1666.0	1081.0
12	1741.0	1052.0	1000.0
13	1818.0	2222.0	900.9
14	1299.0	1520.0	1052.0
15	1176.0	1250.0	1111.0
16	2222.0	1212.0	714.0
17	1156.0	1058.0	966.0
18	1000.0	919.0	1149.0
19	1086.0	909.0	909.0
20	1438.0	1117.0	966.0
21	1428.0	1539.0	1450.0
22	1176.0	909.0	1000.0
23	1538.0	909.0	1000.0
24	1111.0	1111.0	800.0
25	634.0	888.8	806.4
26	623.0	614.0	666.0
27	689.0	666.0	660.0
28	893.0	769.0	834.0
29	773.0	769.0	975.0
30	869.0	741.0	667.0
31	952.0	970.0	938.0
32	1149.0	1129.0	1183.0
33	960.0	938.0	925.0
34	1290.0	701.0	909.0
35	950.0	740.0	800.0
36	636.0	579.0	676.0
37	395.0	1000.0	*
38	*	*	*
39	896.0	813.0	*
40	833.0	1481.0	*
41	815.0	1111.0	*

*No estimation.

appears in the thoracic duct as an emulsion which is eventually emptied into the blood. The portion of fat not absorbed by the lacteals enters the portal circulation directly as a fine suspension. This fat

is then slowly removed from the blood stream to be stored up in the organism as depot fat, in its original form, for one type of fat cannot be converted into another type. Later on, the cells of the body, especially the erythrocytes, take up this fat from the plasma and transform it into lecithin[10] which is an intermediate product in fat metabolism. Fat is also formed from sugar. This is the specific body fat and is stored in the connective tissues and liver until it is utilized. Then, there is a small percentage of a fat protein combination to be considered. In malignancy, with its attending cachexia, so common in the majority of cases, digestion and absorption of fats are normal, but there is very little, if any, fat storage. It is difficult to arrive at a general average of the normal limits for the total fats in the blood. So much depends on the time of collection of blood in relation to meals, the amount and type of food, and the rapidity of digestion. However, as the bloods in this series were collected between nine and ten in the morning, one-half hour after the roentgen-ray exposure, and finally twenty-four hours afterward, we shall consider 700 mg. as being the normal amount of total fats.

Of forty-one cases studied, thirty-four, or 83 per cent., showed a varying excess of total fat in the blood before exposure to the roentgen rays. One-half hour after exposure to the roentgen rays, the first findings were increased in thirteen cases, and decreased in twenty-eight cases. Twenty-four hours after treatment with the roentgen ray, the first findings were increased in six cases and decreased in thirty cases. Thus, the total fat content was diminished in 83 per cent. of this series of cases after exposure to the roentgen ray and in some cases the decrease was preceded by a slight rise of the total fat quantity.

To what is this due? (*a*) To an inability of the cells to remove this suspension of fat from the blood? In this respect one notices in all cachectic states an almost constant milky appearance of the serum, or a lipemia. (*b*) Or is this low or absent fat storage due to the fact that these cells cannot convert the blood suspension into a state suitable for storage?

Again, we can conclude, as in the case of the fatty acids, that there is a definite increase in the blood fat which is markedly reduced for at least twenty-four hours after exposure to the roentgen rays, but we withhold any further conclusions till we have finished our more conclusive study.

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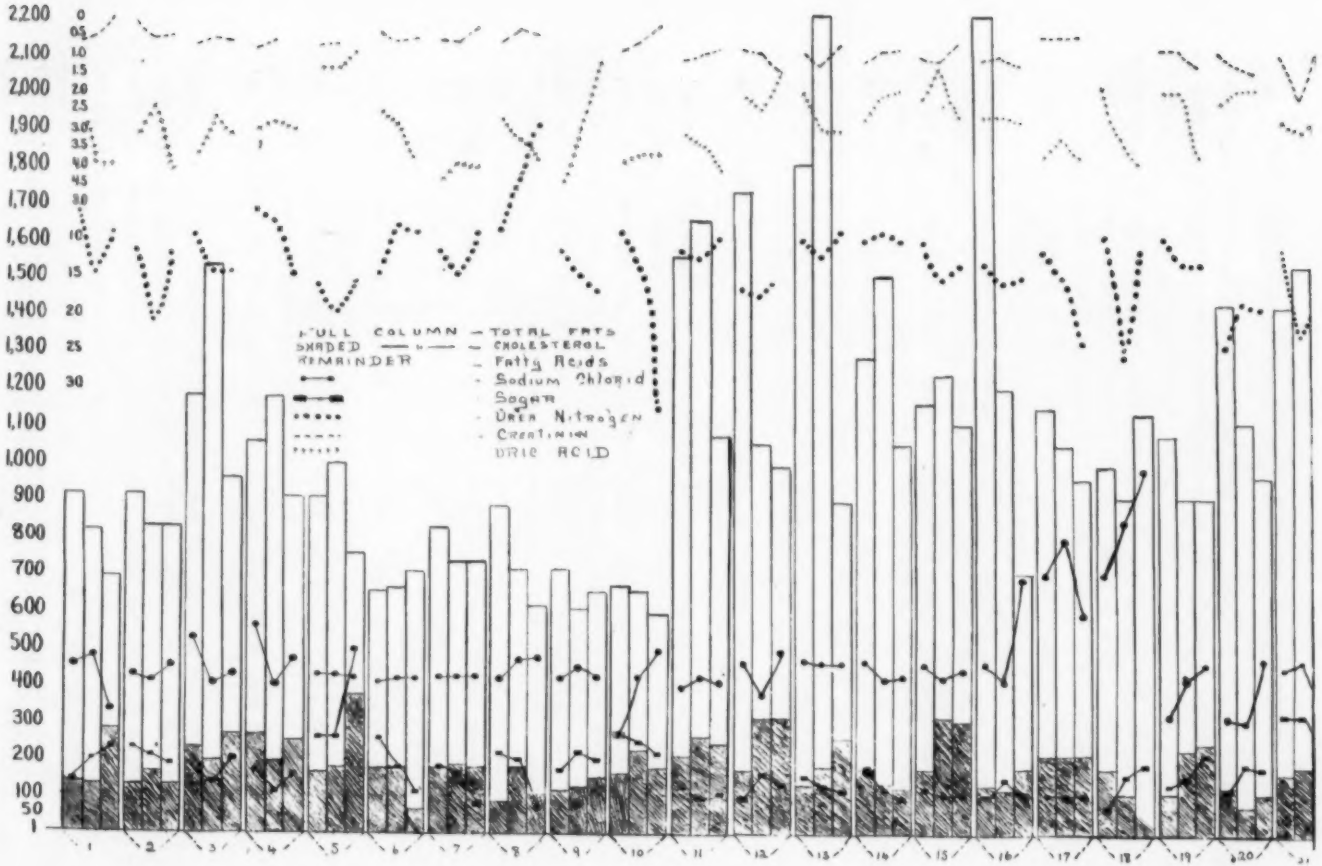
10. Bloor, W. R.: J. Biol. Chem. **24**:227 (March) 1916.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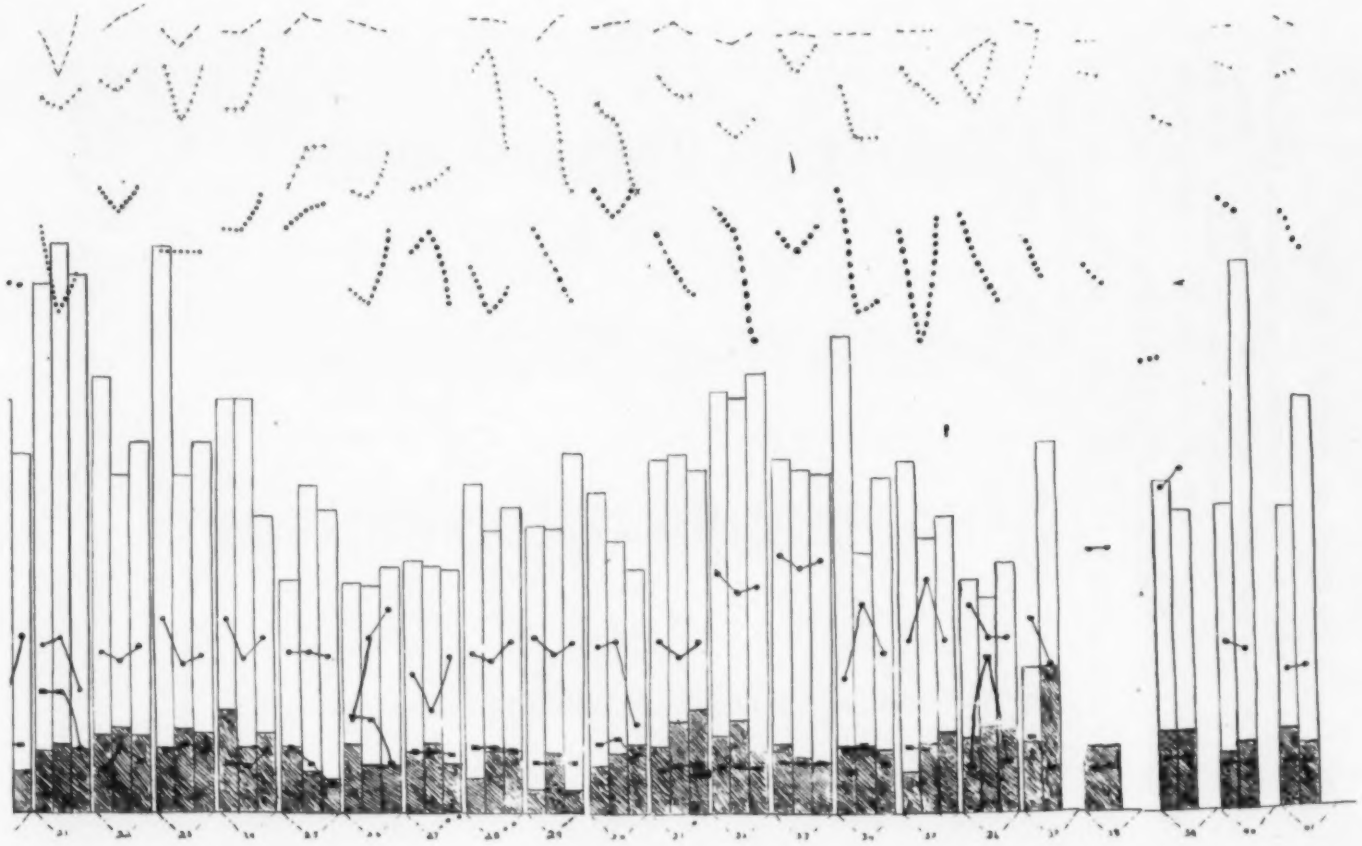

Over a period of long observation we have taken the normal limits of blood sugar to be from 90 to 150 mg. Twenty of our subjects had a blood sugar content of more than 150 mg. which we ascribe to high carbohydrate diet and too little exercise, for the

TABLE 8.—Sugar Content of the Blood
Mg. per 100 c.c.

Number	Before Roentgen-Ray Exposure Per Cent.	One-Half Hour After Roentgen-Ray Exposure Per Cent.	Twenty-Four Hours After Roentgen-Ray Exposure Per Cent.
1	143.0	190.0	235.0
2	222.0	210.0	181.0
3	133.0	142.0	200.0
4	160.0	114.0	153.0
5	266.0	266.0	500.0
6	256.4	178.0	111.0
7	185.0	166.0	80.0
8	222.0	200.0	68.0
9	174.0	222.0	200.0
10	261.0	250.0	217.0
11	133.0	100.0	118.0
12	100.0	160.0	143.0
13	154.0	143.0	133.0
14	182.0	121.0	100.0
15	143.0	121.0	133.0
16	108.0	154.0	127.0
17	117.0	117.0	117.0
18	80.0	154.0	190.0
19	142.0	153.0	220.0
20	123.0	190.4	178.0
21	333.0	333.0	166.0
22	123.0	188.0	143.0
23	164.0	181.0	166.0
24	133.0	123.0	166.0
25	174.0	143.0	87.0
26	266.0	250.0	142.0
27	166.0	166.0	153.0
28	182.0	182.0	175.0
29	143.0	143.0	143.0
30	190.0	200.0	153.0
31	117.0	133.0	137.0
32	130.0	130.0	125.0
33	140.0	140.0	142.0
34	160.0	166.0	133.0
35	188.0	181.8	152.0
36	135.0	427.0	137.0
37	200.0	111.0	.....
38	115.0	121.0	.....
39	143.0	143.0	.....
40	133.0	133.0	.....
41	130.0	130.0	.....

bed patient always shows deficient oxidative powers. We had one diabetic (Case 5) with a glycosuria in the serics. Of the patients studied, several had slight renal lesions, but the majority were normal as to blood chemistry.

Before roentgen-ray treatment, seven patients had hyperglycemia; twenty-one had normal sugar. One-half hour after roentgen-ray treatment, fourteen patients had increased blood sugar; sixteen had decreased sugar, and in ten cases the blood sugar was unchanged. Twentyfour hours after roentgen-ray treatment, fifteen patients had

TABLE 9.—DIASTATIC FUNCTION OF BLOOD

Number	Before Roentgen-Ray Exposure Per Cent.	One-Half Hour After Roentgen-Ray Exposure Per Cent.	Twenty-Four Hours After Roentgen-Ray Exposure Per Cent.
1	11	42	34
2	28	30	22
3	11	12	10
4	8	8	28
5	19	60	60
6	29	14	11
7	30	44	13
8	28	17	17
9	65	12	10
10	28	17	36
11	38	50	21
12	20	34	18
13	13	21	23
14	13	11	37
15	10	6	25
16	46	49	54
19	51	48	17
20	28	62	14
21	47	13	33
22	32	7	28
23	47	44	47
24	26	30	14
25	44	44	18
26	47	22	15
27	47	33	69
28	20	30	38
29	21	3	9
30	34	32	58
34	48	50	40
35	31	43	36
36	38	96	12
37	10	17	..
40	28	28	..
41	40	40	..

increased blood sugar; eighteen had a decreased blood sugar, and in two cases the blood sugar content was unchanged. In the cases in which the blood sugar content was lowest following roentgen-ray treatment, the patients had received the largest doses, so we can say that the roentgen ray increases the oxidation of blood sugar. This is true of any individual whether he has had malignant disease or not. The

degree of oxidation brought on by the roentgen ray is undoubtedly dependent on the degree of hyperglycemia and the duration of the exposure. The effect is not permanent, and a low blood sugar is not further oxidized, but, on the other hand, is increased.

DIASTATIC ACTIVITY OF BLOOD

In one half of the cases the diastatic activity of the blood had increased one-half hour after exposure and in the other cases there was a decrease of diastatic activity. The next day the diastatic activity of one half of the cases studied had increased and in the remainder it had decreased. As the diastatic activity of subjects treated under similar conditions did not show a consistent behavior, we can say that the roentgen rays have no special or permanent effect on the diastatic activity of the blood.

CORPUSCLE AND PLASMA PERCENTAGE

The normal plasm and corpuscle volumes vary between 45 and 55 per cent. Ten c.c. of oxalated blood were centrifuged for five minutes and the percentage of corpuscles and plasma were read directly from the graduations on the tube. The centrifuging was done in each instance at the same rate of speed and for the same period of time. We found that longer centrifuging does not appreciably decrease the corpuscle percentage, and a tube of the oxalated blood standing upright in the icebox gives the same reading of corpuscle percentage.

Before roentgen-ray exposure, ten patients had a low corpuscle percentage; five had a high percentage, and in twenty-one it was normal. Of these twenty-one subjects the corpuscle percentage was decreased in four one-half hour after they were exposed to the roentgen ray and also on the following day; three subjects had an increased corpuscle percentage one-half hour afterward, and five subjects showed an increase the day after treatment. In sixteen subjects the corpuscle percentage remained normal one-half hour after exposure, and in eleven subjects the percentage was still normal the day after exposure. Patients with a low corpuscle percentage were usually anemic. Twenty-four hours after roentgen-ray treatment, eight subjects had a higher corpuscle percentage, fifteen had a decreased percentage and in eleven it remained normal.

Nothing of particular interest was observed in this study, except that the corpuscles quickly settle to their actual volume, and long centrifuging does not pack them any tighter. There is nothing characteristic of the cancer patient in the corpuscle percentage, which

usually varies with the anemia. Some of the patients were unable to drink much water, consequently the corpuscle percentage was high, although there was a marked degree of anemia.

TABLE 10.—PLASMA AND CORPUSCLE PERCENTAGE
Volume percentage

Number	Before Roentgen-Ray Exposure		One-Half Hour After Roentgen-Ray Exposure		Twenty-Four Hours After Roentgen-Ray Exposure	
	Plasma	Corpuscles	Plasma	Corpuscles	Plasma	Corpuscles
	%	%	%	%	%	%
1	52	48	50	50	47	53
2	54	46	54	46	54	46
3	50	50	50	50	53	47
4	50	50	50	50	50	50
5	55	45	55	45	66	34
6	53	47	55	45	55	45
7	62	38	69	31	59	41
8	50	50	55	45	50	50
9	..	..	35	65	32	68
10	52	48	53	47	45	55
11	50	50	50	50	50	50
12	48	52	48	52	..	..
13	50	50	50	50	50	50
14	50	50	..	..	..	..
15	50	50	50	50	..	..
16	48	62	50	50	50	50
17	50	50	50	50	50	50
18	54	46	50	50	50	50
19	72	28	56	44	58	42
20	48	52	48	52	50	50
21	48	52	45	55	45	55
22	48	52	48	52	32	68
23	60	40	50	50	52	48
24	46	54	46	64	50	50
25	62	38	60	40	75	25
26	34	66	27	73	30	70
27	44	56	50	50	41	39
28	40	60	40	60	44	56
29	50	50	50	50	43	57
30	50	50	50	50	50	50
31	28	72	26	74	40	60
32	50	50	40	60	45	55
33	67	43	50	50	50	50
34	57	43	60	40	60	40
35	56	44	58	42	61	39
36	67	33	50	50	50	50
37	57	43	60	40	..	..
38	28	72	30	70	..	..
39	65	35	69	31	..	..
40	50	50	50	50	..	..

SYNOPSIS OF CASE REPORTS

All roentgen-ray treatments were applied directly to the lesion, except in Cases 6 and 25, in which the spleen was treated, and Case 27, in which the abdomen was treated. The control subjects, Cases 12, 16 and 27, were not treated. One patient, Case 23, was given radium

treatment. Cases 22, 24 and 27 were nurses in a fairly good state of health. They received small doses of the roentgen ray.

Case 1 (5462).—Male, age 50; well. Epithelioma of glans penis; removed at operation, Aug. 7, 1917. Lymph nodes in both femoral and inguinal regions enlarged. Uncle had carcinoma of lip. Received seven roentgen-ray treatments during ensuing year. Discharged clinically well. Six treatments had been given before the blood study was made. Filter, 1.4; ma/v, 5/90; time, 7′; distance, 25.5 cm.

Case 2 (5519).—Female; age 60. Progressing adenocarcinoma of left hand for two years, and of right hand for thirteen years; probability of metastatic nodes in lower lobes of both lungs. Definite tumor mass in right lower abdomen. Received three roentgen-ray treatments on hands. Lesions healed, but general condition is growing worse. One treatment was given previous to present study. No filter; ma/v; 10/90; time, 2′ 40″; distance, 20.4 cm.

Case 3 (5533).—Female; age 57; died. Primary carcinoma of left breast. Nodes in supraclavicular and infraclavicular fossae enlarged and movable. Metastatic nodes in left axilla. Maternal aunt had cancer of eye. Received twelve roentgen-ray treatments. The first treatment was given at the time the blood study was made. Filter, 1.4; ma/v, 7/90; time, 10′; distance, 20.4 cm.

Case 4 (5526).—Male; age 65; improved. Epithelioma of left temple. Had paralytic stroke two years ago. Received fifteen roentgen-ray treatments, four of which preceded the one given at the time of the blood study. Filter, 1.4; ma/v, 5/90; time, 10′; distance, 20.4 cm.

Case 5 (5467).—Male; age 61; died. Endothelioma of right parotid region and diabetes. Metastases in submental nodes. Received twelve roentgen-ray treatments, the twelfth being the one given at the time of the blood study. Filter, 1.4; ma/v, 7/90; time, 7′; distance, 20.4 cm. Died in diabetic coma. Necropsy: Chronic interstitial and parenchymatous nephritis; bronchopneumonia; carcinoma, probably epithelioma, of parotid.

Cases 6 and 38 (5357).—Male; age 70 years; died. Epithelioma of left side of head, following injury. Left ear sloughed off. Received thirty-two roentgen-ray treatments before the one given with the blood study. Filter, 1.4; ma/v, 3/90; time, 5′; distance, 25 cm. Necropsy: Abscess of lung and metastatic growths; nutmeg liver; mild chronic nephritis; lymph node tumor metastasis. (This is also Case 38.)

Case 7 (5524).—Female; age 30; improved; exophthalmic goiter. One roentgen-ray treatment given before special study. Filter, 1.4; ma/v, 5/90; time, 7′; distance, 20.4 cm.

Case 8 (5536).—Male; age 31; unimproved. Abdominal tumor. Received one roentgen-ray treatment. Filter, 1.4; ma/v, 5/90; time, 10′; distance, 20.4 cm.

Case 9 (5253).—Male; age 24; improved. Sarcoma of left foot following injury. Received twenty-six roentgen-ray treatments, one preceding that of the blood study. Filter, 1.4; ma/v, 7/90; time, 7′; distance, 20.4 cm.

Case 10 (5513).—Female; age 65; died. Carcinoma of left breast, removed at operation. Metastasis advanced. Four roentgen-ray treatments after operation. Filter, 1.4; ma/v, 7/90; time, 7′; distance, 20.4 cm. Necropsy: Metastases in nodes of mediastinum and hylum of lung. Bronchopneumonia in lungs; cloudy swelling of kidneys and fatty infiltration of liver. Tumor is carcinoma.

Case 11 (5636).—Male; age 58. Tumor of lung, operated and abscess drained. Died three months later. Received seventeen roentgen-ray treatments, eleven before this study. Filter, 1.4; ma/v, 7/90; time, 7′; distance, 20.4 cm.

Case 12 (5027).—Female; age 54; recovered. Carcinoma of left breast, following abscess in breast. Removed at operation. Received twenty-four postoperative roentgen-ray treatments before this study. This was a control case

and the blood was withdrawn at stated intervals without roentgen-ray exposure at the time. Filter, 1.3; ma/v, 14/90; time, 5′, 10″; distance, 20 cm.

Case 13 (5404).—Female; age 50 years; improved. Carcinoma of right breast, removed at operation. Received two roentgen-ray and three radium treatments, postoperative. Roentgen ray, filter, 1.4; ma/v, 7/90; time, 5′; distance, 25.5 cm.

Case 14 (5528).—Female; age 52. Recurrence. Carcinoma of left breast, removed at operation. Ten roentgen-ray treatments and one radium treatment. The radium treatment preceded the first roentgen-ray treatment which was the one of our study. Filter, 1.4; ma/v, 7/90; time, 8′, 10″; distance, 20.4 cm.

Case 15 (5470).—Male; aged 71. Stationary carcinoma of bladder, postoperative, and carcinoma of prostate. Received twenty-two roentgen-ray treatments, twelve before the blood study. Filter, 1.4; ma/v, 7/90; time, 7′; distance, 20.4 cm.

Case 16 (5190).—Male; aged 59; clinically well. Lymphosarcoma of right tonsil. One radium treatment; twenty-eight roentgen-ray treatments. Control case. Blood withdrawn at intervals without roentgen-ray treatment.

Case 17 (5500).—Female; age 62; unimproved. Epithelioma of left shoulder, following injury. Received four roentgen-ray treatments, the one of this study being the first. No filter; ma/v, 10/90; time, 2′ 13″; distance, 20.4 cm.

Case 18 (5494).—Male, age 55. Progressing epithelioma of lower lip. Nodes of submaxillary and submental regions enlarged. Fifteen roentgen-ray treatments given, the first one being at the time of the blood study. Filter, 0; ma/v, 10/90; time, 2′ 13″; distance, 20.4 cm.

Case 19 (5504).—Male; aged 57; no improvement. Epithelioma of left ear. Mother died from cancer of forehead at 60. Received eight roentgen-ray treatments, two before the blood study, and one radium treatment. Filter 0 to 1.4; ma/v, 10/90-7/90; time, 2′ 19″; distance, 20.4 cm. (This is also Case 40.)

Case 20 (5511).—Female; aged 66; well. Epithelioma of nose. Eight roentgen-ray treatments were given, the first one with the blood study. Filter, 0; ma/v, 10/90; time, 2′ 39″; distance, 20.4 cm.

Case 21 (5518).—Male; aged 31; well. Adenocarcinoma of cecum, removed at operation. Received seven roentgen-ray treatments, two before the one with the blood study. Filter, 1.4-2.4; ma/v, 7/90; time, 7′-10′; distance, 20.4 cm.

Case 23 (5507).—Female; aged 44; improving. Carcinoma of cervix uteri. Postoperative. One radium treatment only.

Case 25 (5158).—Female; aged 60; died. Recurrence of carcinoma of right breast, two years after operation. Thirty-three roentgen-ray treatments over spleen; twenty-three before present study. Filter, 1.4; ma/v, 3/90; time, 5′; distance, 25 cm. Necropsy: Metastasis in kidneys, liver, lymph nodes and lung. Suprarenals sclerotic; yellow atrophy of heart.

Case 26 (5522).—Male; aged 35; cured. Angioma of lower lip. Removed under local anesthesia. One roentgen-ray treatment on abdomen. Filter, 1.4; ma/v, 7/90; time, 7′; distance, 20.4 cm.

Case 28 (5520).—Male; aged 52; cured. Epithelioma of left temple, excised. Received two roentgen-ray treatments, the first being at the time of this study. Dose: No filter; ma/v, 10/90; time, 2′ 40″; distance, 20.4 cm.

Case 29 (5488).—Male; aged 46. Epithelioma lower lip; no recurrence. Excised. Two roentgen-ray treatments, the first given at the time of this study. Filter, 1.4; ma/v, 7/90; time, 7′; distance, 25.5 cm.

Case 30 (5475).—Male; aged 51; unimproved. Sarcoma of neck. Fourteen roentgen-ray treatments given, one before this study. Filter, 1.4; ma/v, 7/90; time, 5′; distance, 20.4 cm.

Case 31 (5302).—Male; aged 50; died at home. Fibrosarcoma of left parotid region. Fifty-one roentgen-ray treatments, sixteen of them before present study and one radium treatment. Filter, 1.4; ma/v, 7/90; time, 5′; distance, 20.4 cm.

Case 32 (5223).—Female; aged 58; unimproved. Carcinoma of right breast, two years' duration. Removed at operation. Fifty-three postoperative roentgen-ray treatments; sixteen before present study. Filter, 1.4; ma/v, 7/90; time, 7′; distance, 20.4 cm.

Case 33 (5412).—Male; aged 58; died. Epithelioma. Left face and ear, twenty years' duration. Left ear sloughed with wide ulceration. Eighteen roentgen-ray treatments given, fifteen before present study. No filter; ma/v, 10/90; time, 2′ 13″; distance, 25.5 cm.

Case 34 (5427).—Male; aged 82; unimproved. Epithelioma of left nasal cavity with erosion of left nasal bone. Ten radium and two roentgen-ray treatments given, one before present study. Filter, 1.4; ma/v, 7/90; time, 5′; distance, 20.4 cm.

Case 35 (5501).—Male; aged 65; unimproved. Epithelioma of right eye. Fifty-two years' duration. Received three roentgen-ray treatments, the third at the time of this study. Filter, 1.4; ma/v, 7/90; time, 10′.

Case 36 (5505).—Male; aged 37; died. Melanosarcoma left groin with metastasis. Received one roentgen-ray treatment. Filter, 1.4; ma/v, 7/90; time, 7′; distance, 20.4 cm.

Case 37 (5535).—Male; aged 27, clinically well. Granuloma syphilid with possibly Hodgkin's disease. Received two roentgen-ray treatments here and fifty at another institution, all before the treatment of the present study.

Case 39 (5485).—Female; aged 39; unimproved. Carcinoma of cervix and vagina; postoperative. Received two radium treatments before the roentgen-ray exposure of this study. Filter, 1.4; ma/v, 7/90; time, 35′; distance, 20.4 cm.

Case 41 (5276).—Male; aged 41; unimproved. Epithelioma lower lip. Received eighteen roentgen-ray treatments, three before present study. Filter, 4; ma/v, 7/90; time, 10′.

CONCLUSIONS

Our object in this paper has been to note the effect of roentgen rays on cancer patients, as manifested by changes in their blood chemistry, and to continue investigation of the individual blood factors where it seemed to be indicated.

1. Urea, urea nitrogen and creatinin show nothing characteristic of the cancer patient.

2. The moderate uric acidemia which exists for a short period of time after exposure to roentgen rays is the result of nuclear degeneration but is not especially characteristic of malignancy.

3. The sodium chlorid content of cancer patients is altered neither by the presence of the tumor nor the exposure to roentgen rays.

4. The cholesterol, fatty acids and total fats are generally increased in cases of malignancy. Cholesterol is increased in the blood, but this is not in proportion to the duration of exposure to the roentgen ray or varied as to the type of tumor. The increase of cholesterol in the blood is probably due to cellular autolysis with liberation of cholesterol, induced by the action of the roentgen rays. Fatty acids and total

fats are consistently high in the blood of cancer patients and this increase is reduced by the roentgen rays. We do not care to give any reason or hypothesis for the reduction, as we are at present carrying on further studies along this line.

5. There is nothing in the behavior of the blood sugar or diastatic activity that is diagnostic of cancer. We have noted, however, that the roentgen rays activate the diastase for a short period of time to a greater than normal activity.

6. The plasma and corpuscle percentages were unaltered by the effect of the rays, and of no diagnostic value in cancer.

THE CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS *

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Since the introduction of the colloidal gold test of Lange,[1] numerous reports have appeared in the literature of examinations of the cerebrospinal fluid of large numbers of patients with neurologic diseases of all types.

Characteristic results have been obtained only in neurosyphilis, and the findings of the various types of this disease are now well known. However, the so-called "paretic" gold curve, at first supposed to be pathognomonic of general paralysis, at least within the group of syphilitic disorders, has been obtained in a number of other conditions, among which are lead poisoning, tuberculous meningitis, brain tumor and multiple sclerosis. In the first three of these conditions the curve has not appeared with any regularity, but in the last named it seems to be more than an occasional finding. For this reason, it has been thought worth while to survey the material from this clinic and review the literature, with the object of determining if definite changes in the spinal fluid occur with any regularity in multiple sclerosis.

Textbooks on neurology make scant comment on this point. Such statements as do occur indicate nothing of a characteristic nature. Current literature is also lacking in definite information. In various reports of long series of neurologic and psychiatric cases in which the colloidal gold test has been employed on the spinal fluid, a few cases of multiple sclerosis appear, but the results obtained present no uniformity. Jaeger and Goldstein[2] report, in a few cases of multiple sclerosis (number not stated), a "slight" colloidal gold reaction, there being a faint color change in the first four or five tubes. Three of four cases reported by Eskuchen[3] were completely negative with the Wassermann and colloidal gold tests. The remaining case, which had been regarded as one of multiple sclerosis for years, was at once

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1. Lange: Berl. klin. Wchnschr. **49**:897, 1912; Ztschr. f. Chemotherap., **1**:44, 1913.

2. Jaeger, R., and Goldstein, M.: Ztschr. f. d. ges. Neur. u. Psych. **23**:219, 1913.

3. Eskuchen, K.: Ztschr. f. d. ges. Neur. u. Psych. **25**:486, 1914.

diagnosed as cerebrospinal syphilis in spite of a negative Wassermann reaction in the blood and spinal fluid, because examination disclosed a pleocytosis, positive globulin and paretic colloidal gold curve in the fluid alone.

Flesch[4] reports eight cases, one case completely negative, one case in which the colloidal gold test was slightly positive and other tests were negative, and six cases with the colloidal gold reaction of a paretic type, in which the precipitation was limited more strictly to the first few tubes than is the case in paresis. Kaplan[5] reports two cases, one serologically completely negative, the other with a paretic colloidal gold curve as the only positive finding. In a later paper,[6] reporting eighteen cases, seventeen were negative, and one gave complete precipitation of the gold in the first two tubes.

In this clinic, Miller and his co-workers[7] called attention to the presence of a paretic colloidal gold curve in the three cases of multiple sclerosis which they investigated. These cases are included in the present report.

Oetiker[8] reports two cases, one case with the globulin slightly positive and other findings negative, and one case in which there was no pleocytosis or globulin reaction, but the gold showed partial precipitation in the first five tubes, reaching as high as 3 plus. In Robertson's[9] case, the colloidal gold curve, instead of being paretic in type, showed a "verschieben nach oben," a reaction in the last tubes, reading 0000003355. Lowrey[10] reports one case with a paretic gold curve.

As regards pleocytosis, Rotstadt,[11] in an exhaustive article on the cells of the cerebrospinal fluid, states that in 75 per cent. of his cases of multiple sclerosis (number not given) there was no pleocytosis.

These citations illustrate the status of the subject in the literature. It is obvious that nothing characteristic has been found so far. Of these forty cases, fourteen gave paretic gold curves, twenty-five were completely negative and one case was atypical. Because of the small number of cases reported and the lack of uniformity in the results obtained, it was thought worth while to examine the material from this clinic.

4. Flesch, N. E.: Ztschr. f. d. ges. Neur. u. Psych. **26**: 318, 1914.
5. Kaplan, D. M.: J. A. M. A. **62**:511 (Feb. 11) 1914.
6. Kaplan, D. M.: Ztschr. f. d. ges. Neur. u. Psych., **27**:246, 1915.
7. Miller, Brush, Hammers and Felton: Bull. Johns Hopkins Hosp. **26**:391, 1915.
8. Oetiker: Ztschr. f. klin. med. **82**:246, 1916.
9. Robertson, W. E.: Boston M. & S. J. **174**: 136, 1916.
10. Lowrey: J. Nerv. & Ment. Dis. **46**:186 (Sept.) 1917.
11. Rotstadt, J.: Ztschr. f. d. ges. Neur. u. Psych. **31**:228, 1916.

TABLE 1.—Results of Serologic Examination in Cases of Probable Multiple Sclerosis

Case No.	No. of Cells	Globulin		Wassermann				Gold Chlorid Curve	Diagnostic Possibilities Suggested Other Than Multiple Sclerosis	Final Diagnosis Made before Laboratory Examination
		Ross-Jones	Pandy	Blood	Cerebrospinal Fluid					
					0.25 C.c.	0.5 C.c.	1.0 C.c.			
36353	4	0	+	0	0	...	...	5 5 5 5 5 5 5 2 1 0	Peripheral neuritis	Multiple sclerosis
35531	21	+	++	0	0	1	2	5 5 5 5 5 2 2 1 0 0		Multiple sclerosis
34805	Bloody	+	+	0	0	...	...	5 5 4 3 3 1 1 0 0 0		Multiple sclerosis
34890	7	+	+	0	0	...	...	5 5 5 5 5 5 5 4 2 2 0		Multiple sclerosis
34504	4	+	+	0	0	...	...	4*4*4*4*4*4*3 3 2 0 0	Neurosyphilis	Multiple sclerosis
33638	3	0	0	0	0	...	...	5 4*4*4*4*4*2 2 1 0 0		Multiple sclerosis
37349	70	++	++	0	0	0	0	5 5 5 4 3*3*3 2 1 0	Cord tumor; Erb's disease	Multiple sclerosis
P. M.	27	++	++	0	0	0	0	5 5 5 5 5 5 5 4 2 0		Multiple sclerosis
36361	3	+	+	0	0	0	0	5 5 4 4 4 3 1 0 0 0		Multiple sclerosis
39125	6	++	++	0	0	...	...	5 5 5 4 4 3 2 1 1 0		Multiple sclerosis
38606	7	+	+	0	0	...	...	5 5 5 5 1 0 0 0 0 0		Multiple sclerosis
39141	9	++	+++	0	0	0	0	4 5 5 5 5 5 4 2 0 0		Multiple sclerosis
39275	4	++	+++	0	0	...	...	5 5 5 5 5 4 2 2 1 0	Neurosyphilis	Multiple sclerosis
39271	6	0	+	0	0	...	...	4 5 5 5 3 2 1 0 0 0		Multiple sclerosis
40963	5	++	++	0	0	0	0	5 4*4*3 1 0 0 0 0 0		Multiple sclerosis
41353	2	+	+	0	0	0	0	5 5 5 5 5 5 2 0 0 0		Multiple sclerosis
41986	2	+++	+++	0	0	0	0	5 5 5 3 1 0 0 0 0 0		Multiple sclerosis
40021	1	+	++	0	0	0	0	3*3*2*3*1 0 0 0 0 0		Multiple sclerosis
38831	14	±	+	0	0	0	0	1 1 3 3 3 1 0 0 0 0	Hereditary ataxia	Multiple sclerosis (?)
36724	8	±	+	0	0	...	...	1 2 2 3 3 1 1 0 0 0	Combined sclerosis; brain tumor	Multiple sclerosis (?)
37131	6	++	++	0	0	...	...	1 2 2 3 3 4 3 0 0 0	Disseminated myelitis	Multiple sclerosis (?)
39089	7	0	±	0	0	...	...	0 0 0 0 1 0 0 0 0 0		Multiple sclerosis (?)
39805	6	±	±	0	0	0	0	1 1 2 2 1 0 0 0 0 0	Tabes (syphilitic ulcers ?)	Multiple sclerosis (?)
40064	15	0	+	0	0	0	0	1 1 0 0 0 0 0 0 0 0	Spastic paraplegia (cause ?)	Multiple sclerosis (?)
41359	12	0	0	0	0	0	0	0 0 0 1 0 0 0 0 0 0		Multiple sclerosis (?)
38748	3	+	+	0	0	...	...	1 1 2 2 1 0 0 0 0 0		Multiple sclerosis
35096	2	0	0	0	0	...	...	2 2 2 2 2 1 1 0 0 0		Multiple sclerosis
P.913	80	0	+	0	0	...	...	0 0 0 0 0 0 0 0 0 0	Encephalomyelomalacia disseminata multiplex	Multiple sclerosis (?)

Since the introduction of the colloidal gold reaction, there have been in Johns Hopkins Hospital twenty-eight cases in which complete serologic examinations were made, and in which the clinical diagnosis was either certainly or probably multiple sclerosis. The results are presentetd in Table 1.

Examination of Table 1 reveals the fact that in sixteen cases there was a pleocytosis, considering any cell count larger than five to be abnormal. In twenty-five cases globulin was detected, the amount being large in ten cases. Blood and spinal fluid Wassermanns were completely negative, except for one doubtful reaction with 1.0 c.c. of spinal fluid (which can be regarded as a nonspecific reaction). The gold curve was paretic in type eighteen times; syphilitic three times and negative seven times.

These figures become more striking when the validity of the clinical diagnosis is considered. It will be noted from Table 1 that the definite diagnosis of multiple sclerosis had been made without reserve twenty times before the laboratory examinations were made, and that it was questionable in the remaining eight cases, in which it was made solely as the best possibility. It is without the scope of this paper to discuss the clinical aspects of the disease. Suffice it to say that the diagnosis is often by no means made easily, and that in many cases, unless the patient is observed over long periods of time, it must remain in doubt. Taking these facts into consideration, Table 2 shows the number of cases in which pathologic findings occur in the two groups.

TABLE 2.—SEROLOGIC FINDINGS IN TWO GROUPS OF CASES

Diagnosis	Number of Cases	Pleocytosis of More than 5 Cells	Globulin			Wassermann		Gold Curve			
			Strongly Positive	Positive	Negative	Positive	Negative	Paretic	Syphilitic	Atypical	Negative
Multiple sclerosis...	20	8	9	9	2	0	20	18	0	0	2
Possible multiple sclerosis.....	8	8	1	6	1	0	8	0	3	0	5

Thus, in twenty cases of multiple sclerosis, a paretic gold curve, together with a positive globulin reaction, appeared in eighteen cases, or 90 per cent. This average is high enough to exclude the assumption of a merely occasional accidental finding of such a curve, and leads to the suspicion that in the other eight cases, diagnosed as being probably multiple sclerosis, the diagnosis is at fault, rather than the negative findings.

Excluding the rare cases of lead poisoning, tuberculous meningitis, etc., in which a paretic gold curve has occasionally been found, there are, therefore, only two diseases in which this type of curve occurs

with constancy, parenchymatous neurosyphilis and multiple sclerosis. There is usually no cause for confusion between these two, the diagnosis of neurosyphilis being in most cases clear enough from history, symptoms and clinical findings. If these fail to establish a definite diagnosis, one can fall back on the blood and spinal fluid Wassermann reactions. One or both of these will be positive in neurosyphilis; in fact, whenever a paretic gold curve is found in syphilis, the spinal fluid Wassermann is, so far as is known, always positive, with the single exception of long treated cases, in which the Wassermann becomes negative before the colloidal gold test.

As for the explanation of this reaction it is probably, as Felton[12] suggests, "an estimation of the albumin globulin content of the cerebrospinal fluid, rather than a specific reaction for any one lesion of the nervous system." This, of course, leaves unexplained why in neurosyphilis, multiple sclerosis and certain isolated cases of other nervous lesions, the albumin globulin content should be altered to the particular proportions necessary to produce a paretic gold curve.

SUMMARY

1. The cerebrospinal findings in twenty-eight cases of multiple sclerosis are reported.

2. In twenty of these cases the diagnosis is clinically certain; in the other eight cases it is clinically doubtful.

3. In the first group, the findings are (a) negative blood and spinal fluid Wassermann (all cases); (b) pleocytosis (eight cases); (c) positive globulin (eighteen cases); (d) paretic gold curve (eighteen cases). In the second group the findings are the same, except for the gold curve, which is syphilitic in three cases and negative in five cases.

4. Together with the clinical evidence, it is believed that the spinal fluid picture is fairly constant, and that, other things being equal, such a picture is a strong argument in favor of a diagnosis of multiple sclerosis. In its absence the diagnosis becomes at least doubtful.

12. Felton, L. D.: Trans. A. M. A., Sect. Path. & Physiol., 1917, p. 73; Bull. Johns Hopkins Hosp. **30**:242 (Aug. 1) 1919.

CAVITY FORMATION AND ANNULAR PLEURAL SHADOWS IN PULMONARY TUBERCULOSIS

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The signs of cavity in the lung, both on physical and roentgenologic examination, have always been a matter of interest and inquiry. The present paper aims to give added information on the subject, based, partly, on the examination and observation of a large number of cases in a tuberculosis hospital.

Some years ago my atttention was drawn to shadows in roentgenograms suggesting cavities, although no physical signs of cavity formation were present, and for a considerable length of time the failure to substantiate by roentgenologic means cavity signs obtained on physical examination has been noted.

This inquiry covers cases with definite cavity formation and its classical signs, cases giving fair clinical evidence of cavity but not proven by roentgenologic methods, and cases giving certain roentgenologic images ranging from true cavity formation to simple pleural thickening, without clinical evidence.

PATHOLOGY

Obviously, the reason for the more frequent occurrence of cavity formation near the apex, in the first and second costal interspaces, is that in the majority of cases the apex is the site of the oldest and most extensive lesions. Usually, where cavitation occurs other than in the region of the apex, the apex shows healed fibrous lesions, and below areas of more advanced and destructive processes without healing are present.

The pathology of tuberculosis is so well known that it is unnecessary to review it in detail. The outline given here is sufficient to appreciate more clearly the process of cavity formation. The process of infiltration, especially if localized, progressing into pneumonia-like areas with secondary pleural changes, or vice versa, should be borne in mind. It is a common experience to find the upper half to the upper third of the lung so firmly bound down by markedly thickened pleural adhesions (more so than at the base) that difficulty is incurred in removing the lung intact. These adhesions are often situated so close to the adherent surface of the lung that they are torn open when the organ is removed. Cavities occur more frequently at the anterior than at the posterior portion of the lung. Cavitation occurring nearer the central portion

of the lung is usually situated in the midst of an infiltrated area, and fibrous tissue plays no part in the outline of the cavity, unless the disease has been protracted, or unless there has been an attempt at healing. When cavitation takes place, the greater portion of one or both lungs is affected, unless there has been definite demarcation of the process by dense fibrous tissue as happens commonly at, or near, the interlobar fissure.

What has commonly been observed in the army hospital is the frequency of the hilus type of tuberculosis, that is, involvement of the middle portion of one lung, extending from the hilus region, secondary to advanced disease of the opposite lung. Cavitation under these conditions occurs just outside the hilus area. If tuberculosis involves both apices simultaneously, or nearly so, in time cavitation may occur subsequently at, or near, both apices. This, however, is not common unless the disease is extensive throughout both lungs.

It is always well to bear in mind that the greater the infiltration of the lung, both in density and extent, all else being equal, the more likely is cavitation to occur; the less the infiltration and the greater the fibrous tissue, the less likely is it that cavitation will occur.

Cavities occur because of softening and necrosis. The size of the cavity will depend on several factors, namely, on the extent of infiltrated or affected tissue; the size of the bronchus leading to the cavity; the amount of bronchial dilatation; the condition of the circulation in the immediate vicinity of the cavity; the position of the cavity where movement of the lung is not marked; whether occurring on the surface or margin, and on the resistance of the individual, or the amount of fibrous tissue produced.

The size and position of the cavity and the amount of pulmonary or pleural disease surrounding or covering it affect the diagnosis, provided other conditions (as will be taken up later) are taken into consideration. Recent cavities occurring in the rapid, acute cases have seldom a limiting membrane or lining; their walls are usually irregular and congested.

Cavities occurring in the chronic type of cases have, in most instances, a limiting fibrous membrane; the greater the resistance and chronicity of the case, the more markedly evident is the membrane or fibrous wall. These walls are usually covered with abundant thick pus but are themselves smooth and regular. The larger cavities are commonly traversed by fibrous bands, usually enclosing a blood vessel. Cavities of various sizes distinctly separated from each other may surround the larger cavity. The cavitation with irregular congested outline occurring in tuberculosis is closely simulated by the large abscess cavities which occur in nontuberculous cases. The largest cavities are most often found affecting the upper lobe, the interlobar thickening

forming a substantial lower wall or base to the cavity. Cavity formation may, of course, affect the whole lung, leaving only a very thin pleural sac containing abundant pus and often fluid.

Cavities may heal either through calcification or fibrous tissue formation. Healing depends, however, on the general systemic condition of the patient, the amount of resistance to infection, the stage of the disease, the character of the pulmonary changes, the position of the cavity and, particularly, on the size of the cavity. Cavities greater than 1 cm. in diameter rarely heal. If healing takes place by calcification, the surrounding walls must contain a certain amount of normal tissue. The circulation must be normal, or at most only slightly impaired. Should healing take place by the formation of fibrous tissue, which is the more common reparation process, then the same conditions must be fulfilled. Under these circumstances the fibrous tissue may contract and obliterate the cavity, giving rise to an increased density of tissue. This evident density of tissue frequently may be diagnosed erroneously by the radiogram as infiltration. When healing takes place by the formation of fibrous tissue cavities may be separated completely from the surrounding tissue and cavities with smooth walls and outline may persist. This occurs most frequently in semichronic cases where healing and destruction of tissue take place alternately over a long period of time and where the cavities are situated near the pleural surface.

Thickening of the pleura, which occurs in the greater percentage of tuberculous cases, plays an important rôle in the size, shape and outline of cavities situated near the surface and in their healing and diagnosis.

REVIEW OF LITERATURE

Laennec's work and Kingston Fowler's study are not included as they are sufficiently well known. Ewart[1] gives the occurrence of cavities in the following ratio and position:

At the apices	282
In the dorsal axillary line	227
In the mammary region	189
In the sternal region	61
At the base	32

Allyn[2] states that cavities occur more frequently anteriorly, from the apex to the interspace. Foggie[3] reports a case of pulmonary tuber-

1. Ewart, W.: Croonian Lectures, 1882.
2. Allyn, Herman B.: The Diagnosis of Tuberculous Cavities in the Lung, Am. Med. **9**:190, 1905.
3. Foggie, W. E.: A Case of Pulmonary Tuberculosis with Whole Lung as One Cavity, Edinburgh M. J. **6**:339, 1911.

culosis with the whole lung as one cavity and calls attention to the fact that it was erroneously diagnosed as a pneumothorax. In the same case the left lung also had a small cavity. The postmortem examination showed the lung surface covered with a thickened pleura which was densely adherent to the chest wall. Total destruction of the lung tissue resulted in the formation of a cavity in which a small amount of purulent material was present. Foggie also quotes cases cited by Louis in which three-fourths and four-fifths of the lung was destroyed. He also cites cases reported by Stokes and Ewart, in which there was loss of the whole lung, and twenty-five cases reported by West, in which the size of the cavity in every instance was not less than one half lobe.

Rieder[4] mentions the importance of determining the frequency of cavities, their location, size, changes in time (chronicity) and progress to other cavities, emphasizing the superiority of roentgenographic diagnosis over clinical diagnosis.

Mayer[5] draws attention to the difficulties of collapsing the lung when the cavities are high up in the apical region, and this obviously depends on the pleural adhesions between the lung and the thoracic wall.

Norris[6] calls attention to the obscurity of cavity signs which may be due to a thickened pleura. Cavities, he says, are more frequently overlooked than diagnosed as present when they are really absent. On the other hand, Mantoux[7] reports that in a number of cases of lung cavities, bacilli were difficult to demonstrate and concludes that in many cases in which tuberculous cavities exist a relatively small number of tubercle bacilli is present. Fishberg[8] considers that the acuteness and the duration of the process are two factors of importance in diagnosing tuberculous cavities. In chronic cases he calls attention to cavities with fibrous encapsulation and says that they always drain into a bronchus. As proof of this statement, he says that large numbers of bacilli are always found in the sputum. He also states that large cavities may shrink and that they are often obliterated by granulation tissue or by calcification. In his opinion, cavities may be an indication of the chronicity of the disease, which in my experience is not necessarily the case.

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4. Rieder, H.: Kavernen bei Beginnender, und bei Vorgeschrittener Lungentuberkulose, Fortschr. a. d. Geb. d. Röntgenstrahlen **16**:1, 1910.

5. Mayer A.: Die Behandlung der Kavernosen Phthisie durch Extra-und Intrapleurale Pneumolyse, Deutsch. med. Wchnschr. **39**:2347, 1913.

6. Norris, George W.: The Differential Diagnosis Between Incipient Pulmonary Tuberculosis, Healed Cavities and Non-Tuberculous Fibrosis, New York M. J. **80**:103, 1904.

7. Mantoux, C.: Les Tuberculoses Cavitaires Paucibacillaires, Ann. de méd. **5**:307, 1918.

8. Fishberg, Maurice: The Prognostic Significance of Tuberculous Cavities in the Lungs, New York M. J. **101**:1310, 1915.

Aimard[9] contributes an excellent report on silent cavities and false cavities. He emphasizes the fact that many cavities which occur in the full pulmonary field and are as large as a hen's egg, although seen roentgenographically, may never give physical signs. He quotes Grancher, who insists that certain conditions and their combinations must exist in order that a cavity be diagnosed by auscultation. The cavity must not be smaller than that of a small nut; it must contain a certain volume of air predominating over solids and liquids; the walls of the cavity must be covered by tissue that is dense and yet elastic enough to reflect the sounds; finally, the cavities must not be situated too deeply or be covered by bronchi. Aimard and also Tecon[10] believe that the left lung is affected more frequently than the right. They have reported 323 cases with cavities; on the left in 205 cases and on the right in 118 cases. The left apex is always affected. The left base is very rarely affected. On the right side, however, any portion of the lung may be affected with equal frequency. In every case the Koch bacillus was found in the sputum.

Lamy[11] reports the case of an aged adult with a cavity in each apex. This case is interesting, first, because of the marked involvement of the tracheobronchial glands, some of which had become partially softened, and, secondly, because death was the result of an acute laryngeal and tracheal attack following a marked tuberculous destruction of these structures.

In an article of unusual merit Pallasse and Roubier[12] review the question of tuberculous cavities at the base of the lung. This does not include cavitation of the base as an extension of the process from the apex downward; it includes only those cases where cavitation occurs first of all at the base, in the middle or lower part of the lower lobe, the process predominating there. These investigators quote the opinion of Laennec, Louis Walsche and Jaccoud regarding the rarity of base cavities. These authors hold that cavities of the base occupy exclusively the left base and are of occupational or pleural origin. Fagge believes that a tuberculous process never extends from the base upward and that tuberculosis of the base is better described as a chronic pneumonia. Percy-Kidd found in 412 consecutive necropsies only two cases of tuberculosis beginning at the base. Pallasse and Roubier also

9. Aimard, J.: Cavernes Muettes Tuberculeuses et Fausses Cavernes du Poumon; Diagnostic Radiologique, J. de Radiol. et d'Electrol. **2**:49, 1918.

10. Tecon and Aimard: Gravité comparée des localisations tuberculeuses pulmonaires gauches et droites, Etude de 2,000 cas, Rev. med. de la Suisse Rom. Janvier-Fevrier, 1916.

11. Lamy: Ulcération Laryngo-Trachéo-Bronchique chez un Tuberculeux Cavitaire Mort à la Suite d'une Laryngo-Trachéite d'Evolution Aiguë, Bull. et mém Soc. anat. de Par. **87**:149, 1912.

12. Pallasse, E., and Roubier, C.: Les Cavernes Tuberculeuses de la Base du Poumon, Rev. de la tuberc. **10**:208, 1913.

quote the opinions of Grancher, Rice and others on basal pneumonia processes in which cavity formation or abscesses occur. Obviously, there is no reason to consider such cases here. However, the only cases that are of interest from our point of view are those in which cavities occur in the usual fibrocaseous tuberculosis and in postpleuritic cavitation of the base. In Pallasse and Roubier's five cases the cavitation was found more posteriorly than anteriorly in four cases; in three cases, the walls of the cavity were densely sclerotic and the pulmonary tissue around the cavity showed marked sclerosis. The condition of the surrounding tissue and the presence of tubercles must be taken into consideration before a diagnosis of a tuberculous cavity is made.

Burnand and Tecon[13] believe that cavities occurring at the base are seldom cured. It is their opinion that cavities of the lower lobe most often follow tuberculous pleurisy with infiltration, although they result occasionally from a bacillary splenopneumonia which is undergoing necrosis. The latter sequence is sometimes seen in the progressive type of cases of common fibrocaseous tuberculosis. The authors also agree with other investigators that tuberculous cavitation of the base is not very common, only four cases occurring in the sanatorium. They quote the following figures from Meyer and Leysin: In 1900-1901, of 147 patients only four presented cavity formation at the base; in 1906-1907, of 118 patients only four cases showed a cavity at this point, and in 1907-1908, of 150 patients only three had a similar lesion. Well known anatomic and functional reasons are given to substantiate the opinion that cavities of the base are seldom cured.

Burnand[14] believes that cases of true closed pulmonary tuberculous cavities exist. These cavities are independent of the bronchi or air passages and have no connection with them. Under these circumstances cavitation occurs in the center of a focus, and at the same time stimulates sufficient connective tissue around it to enclose it thoroughly. Caseation and necrosis in the center progress with the thickening of production of connective tissue around the focus. Such conditions have already been referred to in connection with small cavities which frequently become cicatrized.

Walsh[15] reports a case of multiple lesions of both apices in which the cavitations closely resembled cysts. At necropsy these lobes proved to be tuberculous. From the description, the cavitation process probably originated in the pleura.

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13. Burnand, R., and Tecon, H.: Le Pronostic des Tuberculoses Cavitaires de la Base du Poumon, Rev. méd. de la Suisse Rom. **30**:511, 1910. Chalier, M. J.: Tuberculose Cavitaire de la Base, Greffée sur un Ancien Foyer de Bronchopneumonie, chez un Enfant d'un An et Demi, Lyon méd. **113**:743, 1909.

14. Burnand, R.: Existe-t-il des Tuberculoses Pulmonaire Cavitaires Fermée? Rev. méd. de la Suisse Rom. **30**:412, 1910.

15. Walsh, J.: Tuberculous Cavities Resembling Cysts at Apices of Lungs, Proc. Path. Soc., Phila. **13**:161, 1910.

Cavities occurring in the lungs of children are of marked interest and have received a good deal of attention. In the opinion of Ribadeau-Dumas[15a] they are more common than is supposed. He believes with Barbier that cavities are formed at the expense of the primitive tuberculous nodule and that in this case, a fibrous capsule limits the caseous process. Cavities occurring in the lung represent confluent ulcerations appearing in a pneumonia area (Barbier), the walls of which are caseous, enclosed by fibrous tissue like the cavities in adults. Because of the difficulty of diagnosis Ribadeau-Dumas lays emphasis on the roentgenographic examination, as large cavities are invariably diagnosed by this method. Ribadeau-Dumas, Sauvan[16] and Randolph[17] call attention to the habitual absence of physical signs.

Barbier,[18] in analyzing the frequency of cavity formation in pulmonary tuberculosis in infants, comes to some interesting conclusions. In 194 cases of pulmonary tuberculosis, cavities were present in forty-eight cases, giving, in conjunction with the findings of other investigators, a proportion of twenty-nine per 100 tuberculous infants with cavity. Cavities occur more frequently between the ages of three and six months, but often are observed between six and eighteen months. Barbier asserts that the middle anterior part of the lung (that is, the lower part of the upper lobe, or the upper part of the middle lobe) is most frequently attacked. Cavities the result of secondary foci, however, attack the apex by preference and especially on the right side. Barbier, quoting Aine, states that in fifty-two cases forty-four cavities occurred in a single lung and of these thirty-six were limited to a single lobe.

Lhomme[19] emphasizes the deceptive functional and physical signs of tuberculous cavities in infants. He mentions the work of Rilliet, Barthez and Cadet as pseudocavity sounds found in weak, anemic, tuberculous infants with temperature elevation. He emphasizes the lack of expectoration and the presence of hemoptysis in these cases and suggests that under these circumstances search should be made for tubercle bacilli in the feces. Lhomme quotes the following figures on the occurrence of hemoptysis: "Rilliet and Barthez do not find a single case of hemoptysis in individuals under 7 years of age; West

15a. Ribadeau-Dumas, L.: Tuberculose Cavitaire du Premier Age, Bull. Soc. méd. de hôp. de Paris **36**:936, 1913.

16. Sauvan, A.: Caverne Tuberculeuse chez un Enfant du 13 Mois, Marseille méd. **64**:343, 1907.

17. Randolph, B. M.: Case of Cavitation of the Lung in an Infant Dying in the Seventh Month, Washington Med. Ann. **13**:149, 1914.

18. Barbier, H.: A propos de la Tuberculose Pulmonaire chez les Infants de 0 à 2 Ans Fréquence: Formes Cavitaires: Reactions Fibreuses, Paris méd. **19**:109, 1917.

19. Lhomme, H.: Cavernes Tuberculeuses chez les Nourrissons, Rev. Internat. de la Tuberc., Paris **10**:401, 1906.

found four cases; Powell, five cases; Carrie, six cases; Foss, seven cases; Cadet de Gassicourt, eight cases. Henoch and Hendrick believe it is very rare in infants who have not reached the age of dentition. Mantel found fourteen cases."

Weill recorded a tuberculous cavitation of the lower lobe of the left lung in an infant 18 months of age. Enlarged caseated glands were in contact with the cavity. A dorsal Pott's disease also was present in an infant 3 months of age. Collet and Delachanal[20] found at necropsy a cavity involving the whole right upper lobe, and a smaller cavity in the upper part of the lower lobe. Caseated tracheobronchial glands were present on the right side. Pleural thickening with adhesions throughout the upper left lobe was demarcated.

Delearde[21] reports a case of pulmonary cavity in an infant, 10 months of age. There were no signs present which would indicate the very extensive lesions which were found at the necropsy. The necropsy showed an area of caseous pneumonia extending to the middle lobe on the right, in the middle of which a cavity the size of a large nut and filled with caseous pus was found. It is interesting to note, also, that the tracheobronchial glands formed a large mass contiguous with the pneumonic area.

Bergman[22] in a postmortem made on an infant, found cavities in the upper part of the right lower lobe. Similar cavities were present in the lower part of the left upper lobe. These observations are interesting, for cavities occurred on both sides and in unusual positions. The glands were also perceptibly enlarged.

Buddy[23] reports an interesting case in an infant, 3 months old. At the necropsy a cavity the size of a pigeon's egg was found at the root of the left lung; during life, physical signs persisted in this region. Other smaller cavities were found along the vertebral border. It is noteworthy that there was marked enlargement of the glands in chains; some glands at the root of the lung were caseated and had broken down. Adhesive pleurisy was also found.

ROENTGENOGRAPHIC FINDINGS

These will be taken up in the following order: 1. Cavity. 2. True annular shadows. 3. Intrapulmonary annular shadows.

1. *Cavity.*—The basis for the study of cavities from a roentgenographic point of view rests on the postmortem findings and statistical

20. Collet and Delachanal: Cavernes Tuberculeuses chez un Nourrisson de Trois Mois, Lyon méd. **115**:317, 1910.

21. Delearde: Caverne Pulmonaire chez un Enfant de Dix Mois, Echo méd. du nord. **9**:606, 1905.

22. Bergman, H.: Cavernose Lungentuberkulose beim Saügling, Berl. klin. Wchnschr. **52**:77, 1915.

23. Buddy, E. P.: Report of a Case of Pulmonary Tuberculosis with Cavity Formation in an Infant Aged Three Months, J. Missouri M. A. **8**:359, 1911.

data. The point regarding the pathology of cavitation emphasized in the first paper of this series applies, of course, here.

Not all cavities are visible roentgenographically. Size by itself is not important; small cavities, 2 cm. in diameter, are frequently outlined more clearly, are more transparent and are more readily and correctly diagnosed than are larger cavities. It is, therefore, necessary that cavities, irrespective of size, be in such a position that the greater number of factors in diagnosis play a part.

Cavities at the apex usually show more clearly than those at the base, provided the cavities which are compared are similar in size, type, and so forth. However, the fact must be borne in mind that there is less depth to the lung at the apex, and less degree of congestion and secretion with gravity to play a part. Likewise, cavities occurring in or just outside the hilus area are more difficult to diagnose. This is largely because of the depth of the lung. In addition, the picture may be complicated by hilus shadows, congestion or fibrosis. Very often the cavity may be overshadowed by the heart, while occasionally a localized emphysema may be present.

Provided other factors are taken into account, cavities which occur in the full pulmonary field are detected more readily than in those parts of the lungs where the shadows and outlines might be confused with them. Position, therefore, is of importance.

The depth of the cavity—whether it occurs near or under the surface of the lung, or deep in the lung—is important. If situated deep in the lung, then the size of the cavity is undoubtedly an important factor; but the important point is the exact position and size of the cavity in the lung.

The contrast between cavity and lung tissue must be noteworthy; that is, the transparency in the area of cavitation must be greater than the normal transparency in that part of the lung, and, naturally, greater than that of the tissue surrounding it. It is, therefore, important that close attention be paid to the tissue changes surrounding an area of transparency. Usually, the greater the infiltration, or the more solid the lung, the greater the evidence that the area of transparency under observation, surrounded by this area of infiltration, is a cavity. From the roentgenographic point of view this infiltration will show as a more or less irregular heavy density greater than the usual mottling. If the density is more even and, perhaps, more opaque, then, in all probability, we are dealing with a pneumonia type of tuberculosis. It is obvious that in speaking of cavity I have in mind the result of necrosis and softening in an infiltrated area. Therefore, one should always bear in mind the pathology of different tuberculous processes when examining roentgenograms for possible cavitation.

The duration of the disease indicates usually what may be expected besides the usual tuberculous changes; frequently repeated healing or breaking down may cause other tissue changes: fibrosis, for instance, or if the surface of the lung is involved, pleural changes and in consequence, extra shadows and increased density with numerous outlines. Under these additional conditions the transparency of the suspected area will be lessened and its outline confused. The transparency of the cavity will vary just as much as the tissue density around it. This will depend (apart from the factors already mentioned) on the amount of air in the cavity. It must be in greater amount than the secretion or fluid present. The greater the amount of fluid present, the less likely will it be seen, and vice versa.

If the cavity is large and the secretion abundant, change of position of the patient from the prone to the upright posture will bring about a change in density or of fluid level. The lower portion of the cavity will then be denser than the upper portion and the upper outline will be clearer. The transparency of the area and the surrounding tissue density also may vary from week to week, may vary with inspiration and expiration as seen under the fluoroscope, and will, of course, vary if acute conditions are superimposed which will produce congestion and, perhaps, added secretion.

It is impossible to diagnose cavities when the density of the lung around the cavity (that is, back, front, or back and front of the cavity) is greater than the transparency. This is especially true if the cavity is small or filled with secretion.

The outline of cavities or areas suspected of being cavities is of diagnostic importance, but only after the above points have been considered. Cavities may have a clear cut, sharply demarcated outline, clearly differentiated from the surrounding tissue; or they may have an irregular, obscure outline that fades into the surrounding lung substance. The first condition usually indicates a fibrous wall; the second, cavity with continued destruction of lung tissue without definite walls or fibrous tissue outline. The first type of cavity is usually chronic, although the reaction of the lung tissue may be quite marked in acute self-limiting cases. In those cavities with a fibrous wall one can also invariably find shadows indicating fibrous tissue elsewhere in the lung (Table 1). Under these circumstances one must particularly take into consideration the shadows produced by thickened pleura, the outline of which may be confused with the fibrous wall outline of a cavity or cavities. This is especially true if the outlines of several cavities are superimposed one on another. These cases are most often easy of diagnosis, provided one can definitely eliminate shadows produced by the pleura. This point will be taken up later.

TABLE 1.—Roentgenographic Findings in Cases with Cavity

No.	Tuberculosis				Thorax		Rib Spaces		Angle			Cavity Position	Shape	Size in Cm.	Outline	Transparent	Semiopaque	Opaque	Fibrous Bands	Fibrous Outline	Infiltration	Mottling	Calcification	Anterior Posterior
	Right-Left	Advanced	Moderate	Incipient	Symm. Asym.	Long Broad	Narrow	Wide	Right	Gradual	Acute													
2F	..	..	+	..	Asym.	L-Sl.B	..	+	+	..	..	Left apex; ? rt.	Circ.	5×4½	Reg.	+	..	..	—	Sl.	Sl.	+	—	A-P
6D	Adv. rt.; ? lt.	..	..	..	.....	+	+	..	..	+	..	Minute sponge-like annular shadows throughout right upper and middle	All oval	Average from 2 to 3 mm.	Sharp	..	+	..	—	+	+	+	—	A-P
7H	R	+	..	..	.....	+	..	+	..	..	+	1st rib, left	Circ.	5½×5½	Sharp	+	..	..	Light	Sl.	+	+	—	A-P
17O	..	..	..	..	Asym.	Long	+	..	..	+	..	2d rib up, rt. 3d rib up, lt.	Oval and circ.	3 cm.+	Def.	+	..	..	+	+	+	+	—	A-P
46G	R-L	R	L	.	.....	+	..	+	..	+	..	Several rt. and lt., 2d space up	Oval and circ.	2 cm. and more	Indef. and sharp	..	+	..	+	+	Sl.	+	—	A-P
70F	R-L	R	L	..	Asym.	Long	..	+	..	+	..	3d rib up, mult.	Ind.	1 cm.+	Indef.	..	+	..	+	+	+	+	—	A-P
71A	..	+	..	..	.....	Long	+	+	..	+	..	Apices	Ind.	Indef.	Indef.	+	..	..	Indef.	Indef.	+	+	—	A-P
96B	R-L	R	L	..	.....	.....	..	+	..	..	+	Multiple, 3d rib up	Ind.	1 cm. and more	Indef.	+	..	..	—	—	+	+	—	+
123S	R-L	+	..	..	+	.....	..	+	..	+	..	3d rib to 1st rib	Irr. oval	5×5	Dull	+	..	..	+	+	—	—	..	+
125S	R-L	+	..	..	+	.....	..	+	..	+	..	Multiple, rt. apex above 1st rib	Ind.	2 cm. and more	Indef.	..	+	..	..	—	Sl.	+	—	A-P
127M	R-L	R	L	..	.....	.....	..	+	..	..	..	2d rib up, rt.	Oval	2½×2½	Dull	+	..	..	+	+	—	+	—	A-P
128G	R-L	L	R	..	.....	+	..	+	+	..	..	1st to 3d rib, lt.	....	.....	.....	+	..	..	+	+	+	+	—	A-P
150G	..	+	..	..	Asym.	Long	..	..	..	..	..	3d rib up, rt. multiple; 1st rib up, lt	Irr.	3 cm.+	Sharp reg.	+	..	..	+	+	+	+	..	A-P
170F	.	+	..	..	Asym.	Long	R	L	+	..	..	3d rib up, rt.	Ind.	Indef.	Indef.	+	..	..	Sl.	Indef.	+	+	..	A-P
178S	..	+	..	..	.....	Long	..	+	..	+	..	Left apex	Circ.	6×6	Reg.; def.	+	..	..	..	+	..	..	..	A-P
204T	R-L	+	..	..	.....	+	..	+	..	+	..	1st space, lt.	Irr. oval	.....	.....	..	+	..	+	+	+	+	—	+
225U	R-L	+	..	..	.....	L-B	..	+	+	..	..	Several, 1st and 2d spaces, rt. and lt.	Circ.	6-2-3-1½ right; 1-1½-2 left	Sharp, irreg. right; dull, irreg. left	L	R	..	+	+ R;-L	L	R-L	—	+
226C	R-L	Pneumothorax + right			.....	Long	+	..	+	..	..	Multiple, 1st, 2d, 3d spaces, rt.	Circ. and oval	2 to 3 and more	Sharp	+	..	..	+	..	+	+	—	A-P
227C	..	+	..	..	Symm.	Broad	R	L	+	..	..	Over 1st rib, rt. 2d rib up, lt.	Circ. rt.; ind. lt.	3×3, rt. 5+, lt.	Indef.	..	..	..	..	..	+	+	..	A-P
237D	R-L	L	..	R	.....	+	..	+	+	..	..	Several small	Circ.	1 cm. and more	Dull	+	..	..	..	—	+	+	—	A-P
238Y	R-L	+	..	..	+	.....	..	+	..	+	..	Upper left, mult.	Circ. and oval	1×½1¾ and more	Dull	..	+	..	..	—	+	+	—	+

TABLE 1.—ROENTGENOGRAPHIC FINDINGS IN CASES WITH CAVITY—(*Continued*)

No.	Tuberculosis				Thorax		Rib Spaces		Angle			Cavity Position	Shape	Size in Cm.	Outline	Transparent	Semiopaque	Opaque	Fibrous Bands	Fibrous Outline	Infiltration	Mottling	Calcification	Anterior Posterior
	Right-Left	Advanced	Moderate	Incipient	Symm. Asym.	Long Broad	Narrow	Wide	Right	Gradual	Acute													
390D	..	R	L	..	Asym.	Long	..	+	L	R	..	2d space up, rt.	Circ.	10×9	Sharp	+	..	..	+	+	Sl.	+	..	A-P
396H	R-L	L	R	..	.....	L-B	.	+	L	R	..	Quest. 2d rib, lt.	Ind.	Indef.	Indef.	..	+	..		—	+	+	—	Indef.
400B	..	+	.	..	Asym.	Broad	..	+	R	L	..	Multiple, 3d rib up and over 1st rib	Oval	4×5	Reg.; dull	+	..	..	..	+	+	+	..	A-P
408C	..	+	..	..	.....	Long	+	..	..	+	..	3d rib up, rt.; left apex mult.	Circ. and oval	2 cm.+	Indef.	+	+	..	Sl.	Sl.	+	+	..	A-P
442W	..	Pneumothorax left			.....	L-B	+	..	+	..	..	Multiple; 3d rib up, both sides	Circ. and irr.	3 cm.+	Def. and indef.	+	..	..	Sl.	Sl.	+	+	..	A-P
443S	R-L	..	+	..	.....	Sl.	+	..	+	..	..	2d space, left	Irr. circ.	3×3½	Dull; irreg.	+	..	..	—	—	—	—	—	+
466U	..	+	..	..	Asym	.....	Nar.;	Sh.	+	..	..	Left. 1st space	Circ.	3×3	Def.; sharp	+	..	..	+	Sl.	+	+	+	+
487H	R-L	R	L	..	.....	+	..	+	+	..	..	1st and 2d ribs, rt; later cav. on lt.; pneumothorax 1st space	Circ. and oval	5×4 3×4	Sharp	+	..	..	+	+	+	+	+	A-P
543L	R	..	+	..	.....	L-B	..	+	..	+	..		Circ.	3½×3½ 2½×2	Sl. irreg.	1st	2d	..	Sl.	Sl.	—	Fine	—	+
546E	R-L	+	Miliary		+	.....	+	..	..	..	+	1st and 2d space	Ob.	2×1½	Dull	..	+	..	Sl.	Sl.	Sl.	+	..	P
586S	R-L	..	L	R	.....	+	..	+	+	..	..	3d rib, left	Circ.	3×4	Dull	+	..	..	—	—	—	—	—	+
601M	R-L	+	.	..	.....	+	..	+	..	?	..	Upper and middle, right	Irr. oval	1½×1½ 2 cm.+ 6×6	Dull	..	+	..	Sl.	—	+	+	—	+
602W	R-L	..	..	..	.....	+	..	+	..	..	+	Upper lobes	Oval	6×6 6×4	Dull	..	+	..	—	—	+	+	Sl.	P
638Q	..	+	..	..	Asym. L	L-B	..	+	..	+	..	? rt.; 1st rib, left	Circ.	6×5½	Indef.	..	+	..	+	+	+	+	..	A-P
645H	.	+	..	..	Sym. R Asym. R	Broad	..	+	..	+	..	1st rib, both sides	Oval rt.; circ. lt.	6×4R 5×4, lt.	Reg., rt. Dull, lt.	R	L	..	+	+	+	+	..	A-P
646A	R-L	+	..	..	.....	+	..	+	R	L	..	Middle and lower, right	Ind. and circ.	2 cm.+ 3×2	Dull and sharp	..	+	..	—	+	+	..	Sl.	+
652K	R-L	+	+	..	.....	+	Normal		..	..	+	1st space, rt., mult.; 3d rib up rt.	Oval circ.	4½×4	Dull	+	..	..	..	+	+	+	—	..
656G	R-L	+	+	..	.....	+	Normal		..	..	+	2d space, left	Oval	2×1	Sharp	..	+	..	+	+	+	+	+	+*
687M	..	R	L	..	Asym. R	Long	..	+	L	R	..	Multiple, rt. apex	Ind.	Indef.	Indef.	+	..	..	Sl.	Sl.	Sl.	+	—	A-P
688D	..	+	.	..	.....	Long	+	..	..	+	..	Multiple, lt. apex. 2d rib up	Ind.	1 cm.+ Indef.	Indef.	..	+	..	Sl.	Indef.	+	+	..	A-P
705B	.	L-ap.	..	..	Sym	Long	..	+	+	..	..	Over 1st rib, left	Circ.	3.5×3	Sharp; reg.	+	..	..	..	Sl.	+	+	Sl.	A-P
707N	..	L	R	..	.....	L-B	..	+	..	+	..	Over 2d rib	Circ.	3×3	Sharp; reg.	+	..	..	+	+	+	+	..	+
715M	.	+	..	..	.....	Broad	..	+	..	+	..	Multiple 2d rib, right	Circ.	4×4 1 cm.+	Reg.	..	..	..	..	+	+	+	..	A-P

732S	R-L	+	..	..	+	.....	+	..	+	..	+	Both upper lobes	Many oval and circ. lt; 2 cm. rt.*	5×7 rt. 5×3 lt. 3×3½ lt. 3×1¼ lt.	Dull	L	R	..	R & L	Sl.	+	+	—	A-P
766D		+	..	..	.....	Long	..	+	..	..	+	Multiple, lt. 3d rib up	Ind.	2 cm.+	Indef.	..	..	..	+	Sl.	+	+	—	A-P
768C	.	R	L	..	.....	Broad	..	+	..	+	..	Multiple, right apex	Ind.	Ind.	Indef.	..	+	..	Sl.	Sl.	Sl.	+	—	A-P
769F	R-L	+	..	..	Asym.	Long	+	+	..	+	+	Right, all lobes; left, 2d rib up	Oval circ.	1 cm.+ 3 cm.+	Reg.; sharp	+	..	..	+	+	L	+	—	A-P
780B	..	+-	..	..	Asym.	Broad	L	R	+	..	..	2d rib up, both sides	Circ.	4×4+	Indef.	L	R	..	+	Undet.	+	+	—	A-P
811L	..	+-	..	..	.....	Long	..	+	+	..	..	Multiple, 2d rib up, left; 3d rib up, right	Circ.	2 cm.+	Def.	+	..	..	+	Sl.	+	+	—	A-P
810S	..	+-	..	..	.....	Long	..	+	+	..	+	Multiple, 3d rib up, both sides	Circ.	3 cm.+	Def.	+	..	..	Sl.	Sl.	+	+	—	A-P
830A	..	+	..	..	.....	Broad	..	+	+	..	..	Right apex	Sl. oval	2×1.5	Reg.	+	..	..	Sl.	Sl.	+	+	—	A-P
848T	..	+-	Pneumothorax		Asym.	L-B	+	..	..	..	..	Multiple, right 3d rib up	Ind.	Indef.	Indef.	..	+	..	—	—	+	+	—	A-P
858M	..	+	..	..	.....	Broad	..	+	..	+	..	Multiple, left 3d rib up	Ind.	1 cm.+ Indef.	Indef.	..	+	..	Indef.	Indef.	+	+	..	Indef.
895C	.	+	..	..	.....	L-B	..	+	..	+	..	Multiple, 3d rib up left	Ind.	1 cm.+	Indef.	+	..	..	—	+	Sl.	+	—	A-P
930D	..	+	..	..	Sym. L	Fairly long	..	+	+	..	..	Over 2d rib, rt. 3d rib up, lt.; multiple	Ind.	Indef.	Indef.	+	..	..	+	Sl.	+	+	—	A-P
936L	.	L	R	..	Sym.	Long	..	+	+	..	..	1st space, left	Circ.	3.5×3	Reg.	..	+	..	..	+	Sl.	+	—	Undet.
951G	..	+	..	..	Sym.	Long	+	..	..	+	..	5th rib up, right; multiple	Circ.	4 cm.+	Reg.; sharp	+	..	..	+	+	+	+	—	A-P
960V	..	+	..	..	Asym. L	Long	+	..	+	..	..	3d rib up, left	Circ.	5 cm.+	Reg.	..	+	..	+	+	+	+	—	A-P
975O	.	L	R	..	Sl. Sym. L	L-B	L	R	R	L	..	3d to 1st rib, lt.	Oval	4×6.3×2	Reg.; dull	+	..	..	+	+	Sl.	+	—	+
981W	.	+	..	.	Asym. R	Long	+	+	+	..	..	Multiple, 2d rib up, both sides	Ind.	Indef.	Indef.	+	..	..	+	—	+	+	—	A-P
993P	.	..	+	..	Asym.	Long	..	..	..	+	..	1st space and apex left (?)	Circ.	2 cm.+	Def.; reg.	+	..	..	..	Sl.	Sl.	+	—	+
1002T	..	Pneumothorax + left			.....	Long	.	+	+	..	..	4th rib up, rt.; multiple	Ind.	Indef.	Indef.	..	+	..	..	?	—	+	—	A-P
1004Ç	.	+	..	..	Asym.	Broad	L	R	..	+	..	1st space, right; 3d rib up left	Circ.	2-6 cm.	Reg.; dull	..	..	..	+	..	+	..	..	A-P
1039L	..	+	..	..	.....	Broad	..	+	+	..	..	2d rib up, left	Circ.	3 cm.+	Reg.; dull	..	+	..	Sl.	Sl.	+	+	—	A-P
1086S	..	+	..	..	Sl. Asym. R	Broad	+	..	+	..	..	Multiple, both sides	Ind.	Indef.	Indef.	..	..	..	Sl.	—	+	+	—	A-P
1112M	..	..	+	..	Asym. R	Long	+	..	+	..	..	? Apices	Circ.	½ cm.+	Indef.	+	..	..	+	..	—	+	—	?
1116E	.	L	R	..	Asym. L	L-B	..	+	..	+	..	3d rib up, lt.; multiple	Ind.	Indef.	Irr.	..	+	..	Sl.	..	+	+	Sl.	A-P
1169P	.	R	L	.	Sym. L Asym. R	L-B	..	+	..	+	..	2d rib up, right	Circ.	8.5×8	Dull; irreg.	+	.	..	+	..	+	+	—	A-P
1170C	..	+	..	..	Sym.	Broad	..	+	..	+	..	2d rib up, both sides	Circ	6×7. rt. 2×1.5 lt.	Reg.	L	R	..	Sl.	..	+	+	—	A-P
1181H	..	.	R	L	. .....	Long	..	+	..	+	..	1st space and apex, right	Circ	3.5×4 4×4	Def.; reg.	+	.	.	+	..	Sl.	+	-	A- P
1185C	..	R	L	..	Asym.	R	L	..	+	..	..	1st rib and 1st space. right	Circ	5×5.5	Reg.; dull	..	+	.	.	..	—	+	Sl.	Undet

* More pleural than parenchyma.

TABLE 2.—Summary of the Roentgenographic Findings in Seventy-Four Cases of Tuberculosis with Cavitation Recorded in Table 1

Stage of the Disease—	Cases
Advanced tuberculosis of both sides	45
Advanced tuberculosis of right side only	1
Advanced tuberculosis of left side only	1
Advanced tuberculosis, right; moderate tuberculosis, left	11
Advanced tuberculosis, left; moderate tuberculosis, right	6
Advanced tuberculosis, right; questionable tuberculosis, left	1
Advanced tuberculosis, left; incipient tuberculosis, right	1
Moderate tuberculosis of both sides	5
Moderate tuberculosis of right side only	1
Moderate tuberculosis, right; incipient tuberculosis, left	1
Moderate tuberculosis, left; incipient tuberculosis, right	1
Total	74

Shape of Thorax—	Cases
Broad	25
Slightly broad	1
Long	31
Broad and long	17
Total	74

Rib Spaces and Angle of Ribs—	Cases
Wide rib space and right angle	14
Wide rib space, gradual angle (20+ ?1)	21
Wide rib space and acute angle	6
Wide rib space, angle not given	1
Narrow rib space and right angle	8
Narrow rib space and gradual angle	7
Narrow rib space and acute angle	2
Narrow, right; wide, left; right angle	3
Narrow, left; wide, right; right angle	1
Narrow, left; wide, right; right angle, right; gradual, left	1
Narrow, left; wide, right gradual angle	1
Normal rib space and acute angle	1
Wide rib space; right angle, left; gradual, right	3
Wide rib space; right angle, right; gradual, left	2
Rib space not given, gradual angle	1
Not given	2
Total	74

Position of Cavity—	Right	Left	Both Sides
5th rib and above	1	..	..
4th rib and above	3	..	..
3d space above	1	..	..
3d rib and above	8	15	6
2d space above	1	2	3
2d rib and above	10	6	6
1st space above	4	7	2
1st rib and above	8	5	1
Apex	1	..	1
All lobes	1	..	1
Middle and lower lobes	1	..	..
Upper and middle lobes	1	..	..

Size of Cavity—	Cases
Greatest diameter over 5 cm.	22
Greatest diameter over 4 cm.	9
Greatest diameter over 3 cm.	20
Greatest diameter less than 3 cm.	32
Multiple, indefinite	13

Shape of Cavity—	Cases
Circular	42
Oval	26
Oblong	1
Indefinite	22

Outline of Cavity—	Cases
Regular	20
Irregular	6
Sharp	29
Dull	21
Indefinite	24

Transparency—	Cases
Transparent	48
Semiopaque	32
Indefinite	1

The lung changes usually indicate whether the diagnosis of the second type of cavity is warranted or not. If there is surrounding infiltration, if the case is progressive, if there is absence of fibrous tissue, and if all other conditions are equal, the area of transparency with ragged, irregular outline can be diagnosed as a cavity. This cavity will in all probability either grow larger or other areas will in time be seen, behind, in front of, or on either side of it.

The shape of cavities aids in the diagnosis. Circular or oval areas, even and regular in outline predominate in the majority of cases. A true cavity, especially one with fibrous wall, is seldom anything but oval or circular. In cases where cavity outlines are superimposed one over the other care should be taken that the resulting irregular outlines are not confused with the regular outline of a single cavity. Likewise, outlines of the rib, the border of the scapula or of the mediastinum,

bronchial markings, or bands from a thickened pleura may be confused with the outline of the cavity.

Lastly, the unilateral asymmetry of the thorax must be taken into consideration, contraction of the rib spaces, the increased angle of the ribs themselves from the spine, and the narrow bony apical outline, as well as the total narrowness of the thorax; in short, any appear-

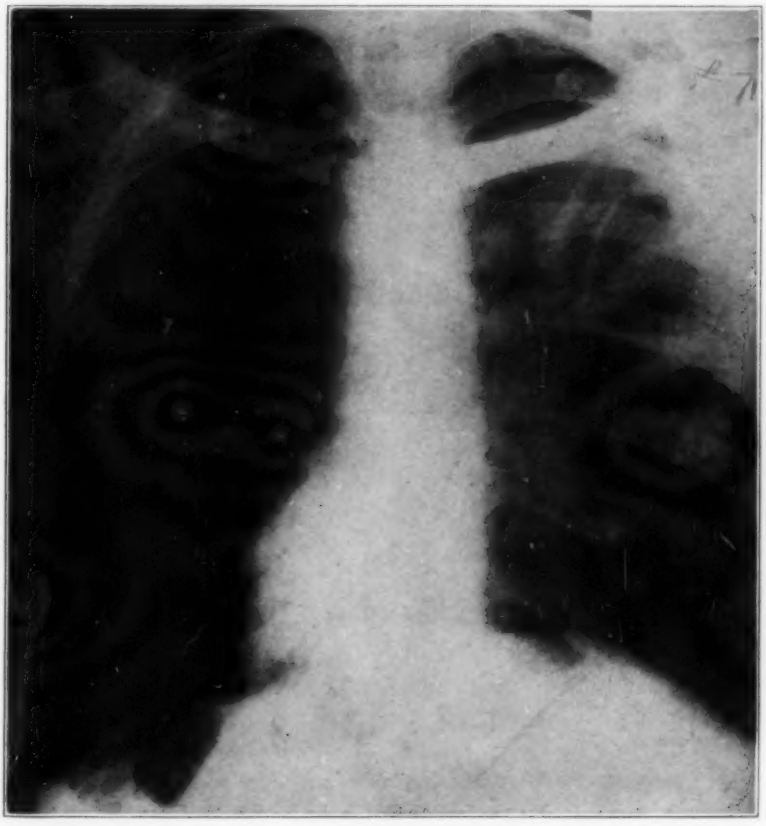

Fig. 1.—Case 71. Roentgenogram of lungs in a fairly early case. There is typical pleural thickening on the right side with annular shadow, not circular. This roentgenogram demonstrates a stage in the development of pleural annular shadows.

ance of the thorax to indicate lack of respiratory effort or lack of lung function, and, therefore, immobilization of the chest wall, especially if in contrast to the opposite side. If there is cavitation at the apex, it is surprising to see the degree of contraction or collapse that takes

place in the thorax wall from the apex to the third or fourth ribs. The physical findings should be included in all cases of cavitation, especially when the roentgenogram fails to give complete or definite evidence.

2. *True Annular Shadows.*—These shadows are produced by the pleura. They have no relation to pulmonary infiltration or softening

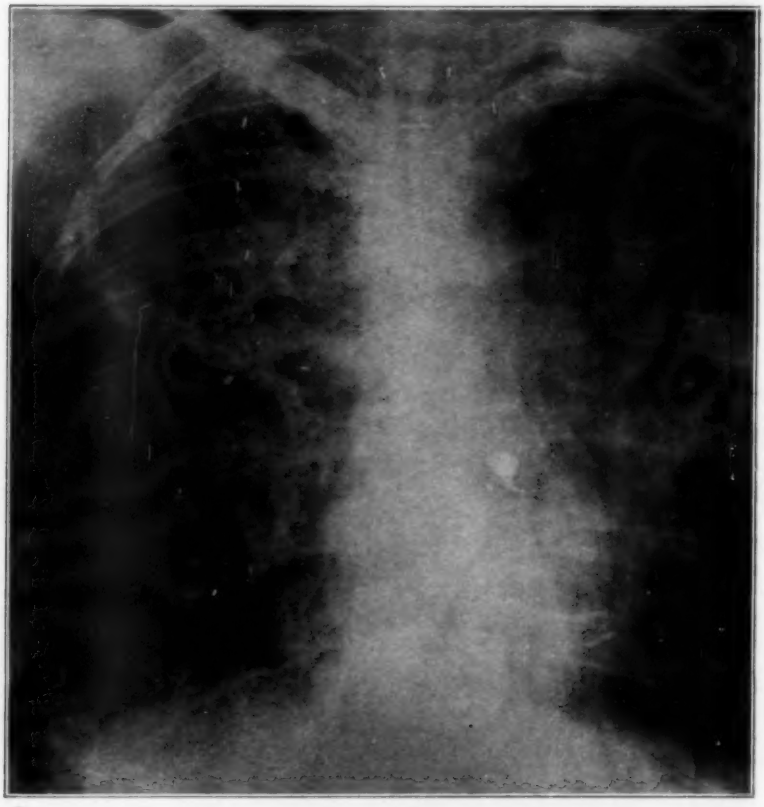

Fig. 2.—Case 225. Roentgenogram of the lungs in an advanced case with large multiple cavitation, not typical and in earlier stages more difficult to diagnose.

and breaking down of lung tissue. It is true that the two conditions may coexist, but it is equally true that pleural changes may be secondary to cavitation, or vice versa. Consequently, if a case is presented in which cavitation is accompanied by a pleural annular shadow, it is generally impossible to differentiate the two conditions (Case 1.

TABLE 3.—Pleural and Bronchial Annular Shadows

Number	Date	Position	Size	Type
1094 C	4/25/19	1st rib, left	3.5 × 2.5	Intrapulmonary Br.
733 D	1/27/19	3d rib up, right	Multiple; indistinct	Intrapulmonary Br.
901 M	4/17/19	2d rib up, right	3 × 3	Intrapulmonary Br.
966 B	3/ 5/19	2d to 1st rib, left	3.5 × 3	Intrapulmonary Br.
71 A	7/ 8/18	4th to 2d rib, right	7 × 5	Pleural
687 M	12/ 6/18	Over 2d rib, right	4 × 2.5	Pleural
1137 J	4/30/19	2d rib to apex, right	Indefinite; several circles; 2+ cm.	Intrapulmonary Br.
1127 P	4/28/19	Left apex	3 × 3; indistinct	Intrapulmonary Br.
994 M	3/13/19	Over 1st rib, right	3 × 2.5	Pleural
993 F	3/19/19	1st space, left	2 × 1.5; indistinct	Intrapulmonary Br.
	and	Over 3d rib, left	3.5 × 3; full field	
	5/ 8/19	Over 4th rib, right	4 × 3	Pleural or intrapulmonary Br.
936 L	3/ 8/19	Over 1st rib, left	3 × 3	?Pleural
479 W	2/17/19	Over 2d rib, left	4 × 3	Pleural
	and			
	4/29/19	Over 2d rib, left	4 × 4	?Intrapulmonary Br.
1096 B	4/25/19	2d to 1st rib, right	5 × 4; indistinct	?Intrapulmonary Br.
1091 B	4/25/19	2d to 1st rib, right	4 × 4; indistinct	Intrapulmonary Br.
1129 D	5/ 1/19	Over 1st rib, left	4 × 4; sl. indistinct	Intrapulmonary Br.
1140 V	4/30/19	3d rib up, left; 2d rib up, right	Multiple small and large circles, diffuse outline	?Cavitation and annular; pleural
455 W	3/14/19	3d space, right	3 × 1.5	Pleural
656 G	11/30/18	2d space, left	Several overlapping 2 × 2 and 1 × 1	Intrapulmonary Br.
1144 H	4/30/19	Apex, left	2.5 × 1.5	Intrapulmonary Br.
852 M	3/19/19	Over 1st rib, left; outer	5 × 4	Intrapulmonary Br.
853 S	3/27/19	1st to 3d rib from hilus, right	5 × 5	Intrapulmonary Br.
828 B	3/ 8/19	2d rib to apex, left	5.5 × 4	Pleural
1009 M	4/13/19	Apex, left	3 × 3	Intrapulmonary Br.
		Apex, right	3 × 3	
668 F	2/17/19	3d to 2d rib, left	2.5 × 2.5	Intrapulmonary Br.
*		3d to 1st rib, right	4 × 4 × 4 (triangle)	
983 D	3/11/19	2d rib, right and left	Several superimposed 2+ cm.	?Intrapulmonary Br. and pleural
B	4/28/19	2d rib to apex, right	Irregular, double circle	Intrapulmonary Br.
1128 K	4/28/19	Over 1st rib, left	3 × 3	Pleural
1181 H	5/ 7/19	Over 3d rib, left; cavity right apex	2.5 × 4	Intrapulmonary Br.
1174 B	5/ 6/19	1st rib, left	3 × 3	Pleural
406 U	5/ 9/19	2d and 3d ribs, right; cavity left apex	4 × 4 and 3 × 3	Pleural and intrapulmonary Br.
369 M	9/ 4/18	2d space, right	1.5 × 1.5	Pleural
661 D	12/7 and 11/18/18*	4th space, left	5 × 5	Pleural
119 F	3/17/19	2d rib and 1st space, right	5 × 5	Intrapulmonary Br. and pleural

* 4th of April and 7th of May, no trace. No emphysema at any time.

TABLE 4.—Summary of Findings Shown in Table 3

Position—	Left	Right
4th space	1	
4th rib and up	1	1
3d space	..	1
3d rib and up	4	4
2d space	1	1
2d rib and up	5	9
1st rib and up	6	1
Apex	3	1

Type—	Cases
Intrapulmonary bronchial	17
Ques. intrapulmonary bronchial	2
Pleural	10

Size—	Cases
Over 5 cm. in greatest diameter	3
Over 4 cm. in greatest diameter	8
Over 3 cm. in greatest diameter	13
Less than 3 cm. in greatest diameter	4
Multiple, indefinite	6

Type—	Cases
Ques. pleural	2
Intrapulmonary Br. and pleural	2
Ques. intrapulmonary Br. and pleural	2

390 D). Under these circumstances it appears that the process of cavitation in the lung is anchored for beneficial purposes by the pleura.

CASE 1 (390 D).—Examined Feb. 17, 1919. A definite annular shadow found in the right upper lobe accompanied by pleural thickening. No evidence of cavitation. Examined again May 19, 1919. Stereoscopic roentgenograms gave an unusual picture of positive cavitation in the right upper lobe, demarcated sharply below by the interlobar fissure, which was seen as a heavy opaque band. Above this band the transparency was marked with great depth and no lung markings. There was absolutely no positive physical signs of cavitation present.

An annular shadow, in most cases, is larger than a true cavity, being generally four or more centimeters in diameter. Consequently, a large size is in favor of its being pleural. These shadows are by no means as common in the apical region as are those of cavitation. Table 3 demonstrates this. These annular shadows are more superficial. They appear to be nearer the surface and usually seem to be on an even plane.

The inner and outer borders of the outline of an annular shadow usually differ more than do those of cavities. The inner border is usually sharply demarcated and smooth, as is found in a cavity with a well formed fibrous wall. The outer border fades off, is usually not demarcated from the surrounding tissue and so differs from the sharp inner border. The transparency of an area within a ring, in a slightly affected lung is, of course, no greater than any other part of the lung. There is also no reason why in an affected lung, say infiltrated, a true annular shadow should give an inner area of transparency. In cases where the annular shadow and lung cavitation combine, the case is different.

Annular shadows are not necessarily of a regular oval or circular outline. The contour depends on the position of the shadow, the duration of the pleurisy and on other physical facts. They are much less liable to be circular than are the majority of cavities. Not infrequently, three-fourths of the circumference of annular shadows is regularly circular, the remaining one-fourth being irregular with an indefinite border. This is more likely to be the case when the pleurisy is extensive. Under the latter circumstances the diagnosis of an annular shadow is usually easier; and also the fewer lung changes there are, the easier the diagnosis of the presence of annular shadows.

Annular shadows are the result of adhesions between the parietal and parenchymal pleural surfaces subsequent to inflammation. Under certain conditions there is an oval or circular arrangement of the pleura to the formation of which the movement of the lung and thorax contributes, resulting in the formation of a central or local pseudo-emphysema. The area around the annular shadow which borders on the shadow represents the more firmly attached or organized pleura. In

an interesting case of a light cortical pneumonia, observed early at the army hospital, a distinct annular shadow over the fourth space in front and in the full pulmonary field was noted. The shadow was at first localized and even but progressively developed into an annular type which later gradually disappeared. The whole process developed during a period of four months and has proved to be tuberculous in origin. The clinical observations agreed with the roentgenographic findings.

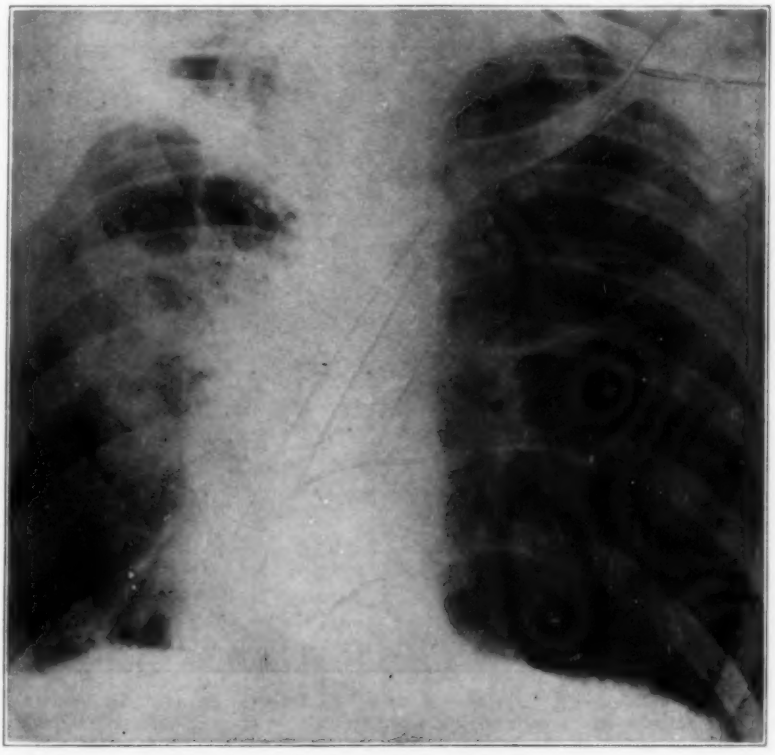

Fig. 3.—Case 707. Roentgenogram of the lungs in an advanced, rapidly progressing case. The atypical annular shadow is more difficult to diagnose. Probably early multiple cavitation was present. Frequent reexamination is important in these cases.

The most important question in the majority of cases is whether the lung condition warrants a diagnosis of tuberculosis. If this is established, then one must determine whether the disease is sufficiently advanced to make the diagnosis of cavity probable. Consequently, the appearance of annular shadows in such cases must have a relation to

the underlying lung condition (Case 1. 390 D). If physical signs are insufficient to establish the diagnosis of cavity, the assumption is warranted that the annular shadow is due to pleural inflammation. From the foregoing it may appear that it is a simple matter to differentiate accurately between cavitation and annular shadows, yet this is not the case. Size, position, lack of transparency, gradual fading of the outer border, evidence of pleurisy, absence of advanced pulmonary changes, and so forth, are aids in differential diagnosis but nothing more.

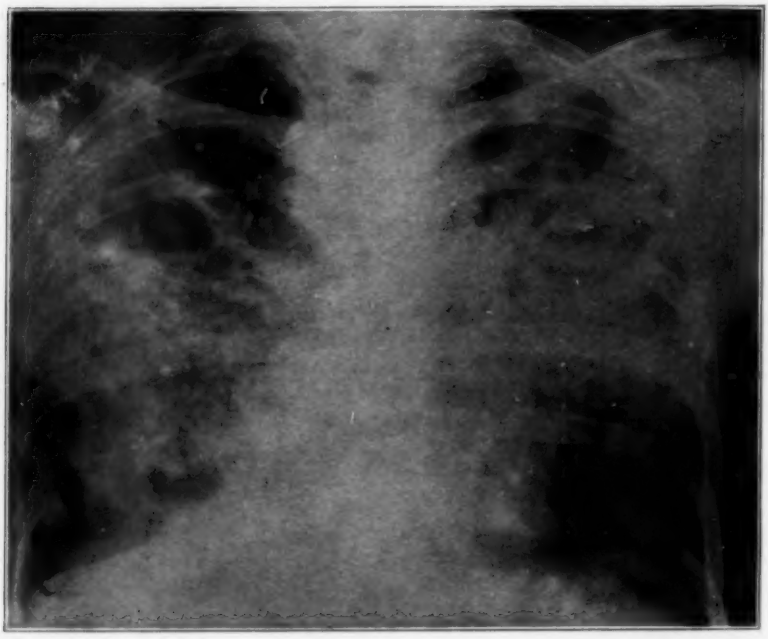

Fig. 4.—Case 811. Roentgenogram of the lungs in an advanced bilateral case showing the presence of a large typical cavity in the right lung and multiple cavitation throughout both lungs.

Just as physical signs disappear in ordinary clinical cases of pleurisy, so in the course of a few months annular shadows also may appear (Case 2. 768 C.). The absence of progressive lung changes in the face of modification in the shadows is added proof that the latter are pleural in origin.

Case 2 (768 C).—Examined Feb. 25, 1919, and a distinct annular shadow was seen at the second interspace on the left. May 19 the patient was reexamined and no evidence of annular shadow was found. The local lung density had not increased although some advance of the disease was seen in both lungs.

3. *Intrapulmonary Annular Shadows.*—In a small percentage of cases these shadows occur in the full pulmonary field. Invariably, they are just outside the hilus area, one border of the ring shading off into the hilus itself. Although very rarely mistaken for cavities, these shadows may easily be confused with pleural annular shadows. Intrapulmonary annular shadows are rarely as regularly oval or circular as true annular shadows. Their walls commonly resemble peribronchial thickening and in the majority of cases a well defined communication is seen between the shadow and bronchi at the hilus or in the full pulmonary field. The inner border of the shadow does not differ from the outer; both are slightly irregular or fuzzy in outline. The transparency of the inner area is no greater than that of other portions of the lung. These shadows can invariably be diagnosed. If closely examined with the stereoscope, it will be found that the medial portion of the shadow, that is, the portion resting on the hilus, is heavier than the distal portion, and that it is definitely bronchial and hilic in origin. The distal portion fades off, and ordinarily the two points which form an arc or the outer half of the annular shadow, are separated.

The stereoscope definitely indicates that intrapulmonary annular shadows are formed by two or more bronchial or root branches, and that they are neither pleural nor cortical in origin. These intrapulmonary shadows are seldom seen either in the second or in the advanced stage of tuberculosis. Indeed, if tuberculosis is present to any marked degree, these shadows are made out with difficulty. They are due to definite fibrous peribronchial changes and do not disappear. With the exception of aiding in ruling out tuberculosis, clinical evidence seldom assists in the diagnosis. A very unusual example of this type of shadow is illustrated in Case 3, 853 S.

SUMMARY

To summarize: There are three conditions which at times may be confused and which make a differential diagnosis difficult or often impossible. These include (a) true cavitation in pulmonary tuberculosis, with and without fibrous walls; (b) true pleural annular shadows, with and without pulmonary disease; (c) false annular shadows of intrapulmonary bronchial origin, occurring in early pulmonary tuberculosis and other chest conditions. These three conditions are illustrated here.

I have shown that a clear understanding of the pathologic processes involved, thorough appreciation of the different clinical signs is needed, and since, in a broad sense, we are less interested in the presence or absence of cavitation than in its affect on diagnosis, treatment and prognosis, it is essential carefully to consider other acute or chronic lung lesions in conjunction with the direct evidence of cavitation.

Apical pleural adhesions are, of course, of much greater weight in the diagnosis of pulmonary lymphatic tuberculosis than are similar changes at the base. However, the mere presence of an apical annular shadow, although it may be due to the same process which occurs frequently at the base, invariably leads to a more serious diagnosis than is warranted. If the movement of the lung at the apex were as great as at the base (all other conditions being equal), probably fewer annular shadows would result from pleural thickening. If tuberculosis of the base of the lung occurred more frequently, we would be led, in a large number of cases, to a different diagnosis than that of mere

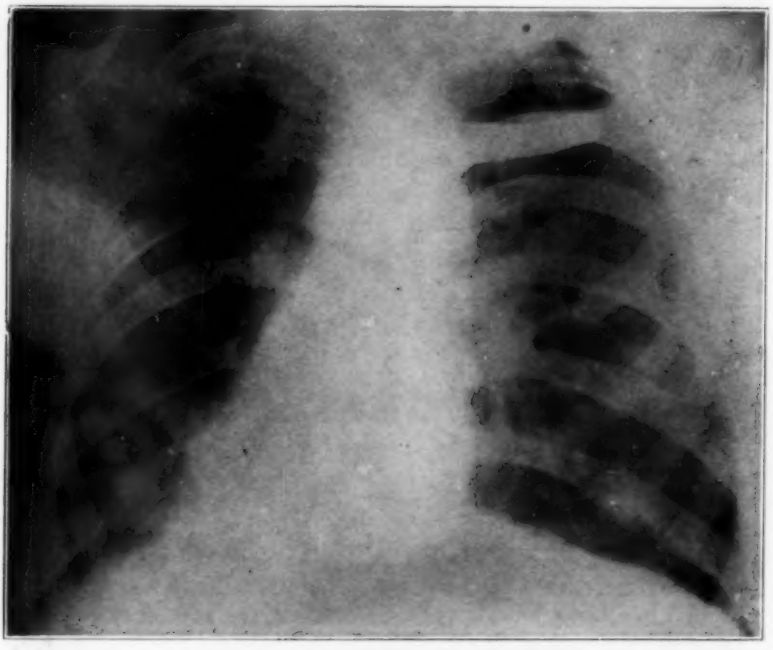

Fig. 5.—Case 828. Roentgenogram of the lungs in an advanced case, showing a large, very typical cavity in the left apex with smaller multiple cavities in the right apex.

pleural thickening. On the other hand, if every annular shadow depended on a cavitation in the lung, then the frequency of lung cavitation would be increased enormously. Under these circumstances the presence or absence of preceding infiltration is unessential.

In many cases distinctly oval or circular areas of transparency which confuse the diagnosis are found. These areas, which are often outlined by bronchial shadows, bony structures, or most frequently by

the hilus, may be mistaken for cavitation, annular shadows or even bronchiectasis; occasionally they are produced by a localized emphysema (Case 119 F. and Case 1131 M.). Finally, the physics of roentgenology and the limitations in roentgenologic diagnosis must be remembered. If acute, congestive conditions prevail, it may be impossible to differentiate the lesions mentioned. Repeated roentgenological and physical examinations are, therefore, clearly indicated.

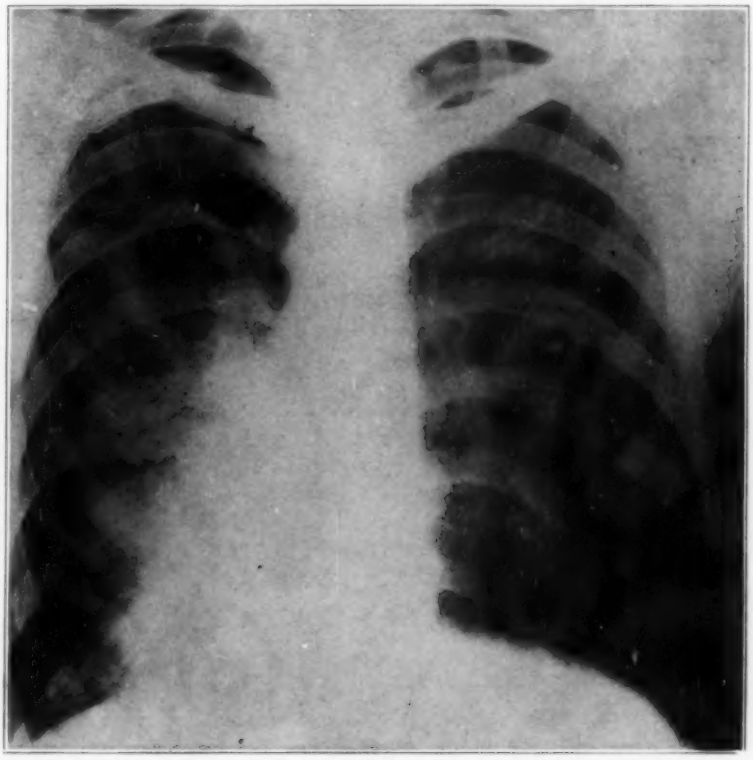

Fig. 6.—Case 840. Roentgenograms of the lungs in a case demonstrating the difficulty often encountered in making a diagnosis of cavity and annular shadow.

CLINICAL FEATURES

The difficulty in determining the presence of a cavity can readily be imagined by a study of the pathologic and roentgenologic findings in this condition. The roentgenologist errs more frequently in failing to diagnose a lesion when it is present than in diagnosing cavitation when it does not exist. Clinically, the reverse is true. A diagnosis of

cavitation is frequently made when no cavity is present. This is no reflection on the clinician, for in both physical and roentgenologic diagnosis there are similar limitations. To illustrate this point the following cases are presented:

CASE 3 (1021 P).—Clinically, this was an advanced case of pulmonary tuberculosis. On physical examination, there were definite signs of cavity, such as whispered pectoriloquy and bronchial breathing. There was an area of hyperresonance on percussion localized over the upper lobe of the right lung. On roentgenologic examination, the right lung was markedly consolidated without evidence of cavitation. Postmortem examination demonstrated the correctness of the roentgenologic findings. It is well known clinically that fluid and consolidation may give some of the signs of cavitation. It is equally well known that large cavities may exist without physical signs.

CASE 4 (390 D).—Clinically this was a case of active pulmonary tuberculosis involving the upper and middle lobes of the right lung and the upper and lower lobes of the left lung. Roentgenograms made September, 1918, and February, 1919, confirmed the clinical diagnosis. A third roentgenographic examination at the end of April, 1919, showed a definite cavity involving the whole upper lobe sharply demarcated by thickened fibrous tissue and interlobar pleura. Clinically, positive signs of a cavity could not be decided until June.

In briefly reviewing some of the literature several points of interest are brought out. Aimard[9] calls attention to so-called "silent" cavities. However, it is not clear whether or not he includes under this heading annular pleural shadows that are not cavities. He divides cavities into three classes; under the third class, he places those in which the contours are effaced, indicating an arresting of the process. These manifest no clinical signs of cavity and their outlines may disappear. "Again," he states, "one sometimes encounters false silent cavities which might be taken for real ones. These are chiefly seated at the right apex."

Paillard and Robert[24] summarize very well the physical findings in cavitation. In large cavities they are as follows: exaggerated sonority; rather frequent cracked pot sounds; exaggerated vibrations; amphoric breathing; sometimes gurgling sounds, which may change with the patient in different positions; pectoriloquy; a clear zone of sound in marked contrast to surrounding tissue, and sometimes a suggestion of Hippocrates succussion splash. Smaller cavities sometimes give intense and diffuse bronchophony.

Grancher believes that the diagnosis of a cavity is not difficult if it be large and contain little fluid, or if it be dry. He holds also that râles may mask the cavernous breathing and that caseous glands may compress a lobar bronchial and conceal the cavity. It has also been shown, as already noted by Aimard, that emphysema and pleural adhesions may interfere with the diagnosis of cavity.

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24. Paillard, H., and Robert, L.: Quelques Points de Séméiologie des Cavernes Pulmonaires Tuberculeuses, Progrés méd. **27**:462, 1911.

Sternberg[25] states that coarse tubular sounds are pathognomonic with the same type of râles found with, or after, coughing. He considers the quantity of sputum important, while a continuous secretion of "suppurating" sputum indicates probable cavity. A quantity of sputum between 80 and 100 c.c. is significant. As is well known by percussion, a change in the quality of the note with the mouth open and when closed suggests cavity. Sternberg's modification of Wintrich's phenomenon gives the following results with the mouth closed, light percussion elicits no abnormal sound. When the mouth is opened

Fig. 7.—Case 853. Roentgenogram of the lungs in a fairly early case with typical bronchial annular shadow extending from the first to the third rib on the right side. This shadow may be seen best by means of stereoscopy.

as widely as possible and uniform vigorous percussion is continued, a tympanitic sound is elicited which decreases as the mouth is gradually closed. Sternberg also emphasizes the importance of the presence of large numbers of acid fast bacilli. The failure to obtain positive sputum is generally against cavitation.

25. Sternberg, A.: Zur Symptomatologie der Lungencavernen, St. Petersb. med. Wchnschr. **35**:626, 1910.

King,[26] reporting on posttussive suction as a constant sign found in cavities, claims that whispering pectoriloquy in his experience is most fallacious. Posttussive suction has a high detached sound heard over certain cavities after coughing. It may vary in depth and intensity. He believes that it occurs most usually in old cavitations where there is a good deal of elastic fibrosis around the cavity. He agrees that firm pleural adhesions favor the production of the sound. It is not heard, however, in every case of cavity, but when heard it is a positive sign.

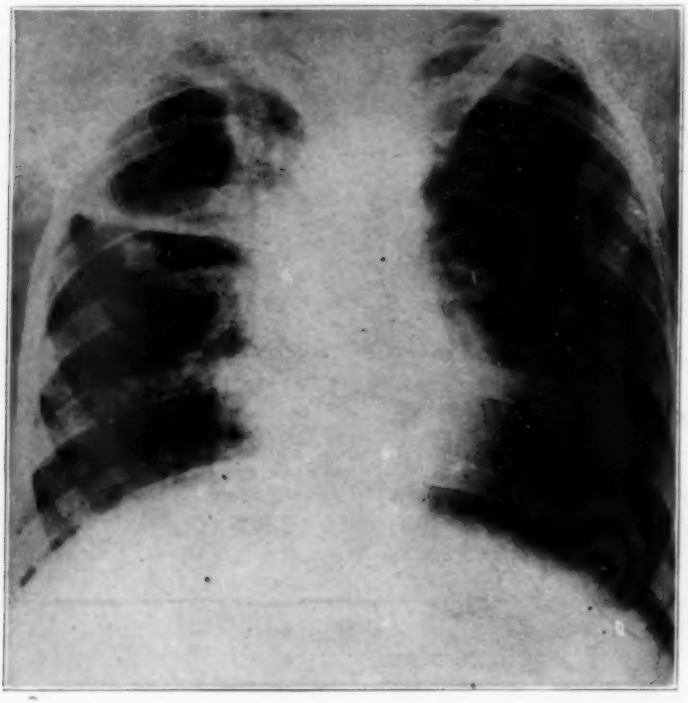

Fig. 8.—Case 960. Roentgenogram of the lungs in an advanced unilateral case. The original upper right lobe involvement is demarcated strongly and sharply by fibrous and pleural interlobar thickening. The large cavity has a heavy fibrous outline.

Norris[6] lays stress on the important and interesting question of the differential diagnosis between incipient tuberculosis, healed cavities and nontuberculous fibrosis. The fine, localized crackling râles which are heard at the end of inspiration and which often disappear on deep

26. King, D. B.: The Value of Posttussive Suction as a Sign of Excavations in the Lung, Internat. Clin., 15 S. **4**:61, 1906.

breathing cannot be confused with the longer, louder metallic clicks heard when a cavity is present. Likewise, the blowing amphoric note and whispered, cavernous pectoriloquy are not readily confused with the suppressed breath sounds, respiratory harshness, or bronchial breathing found in incipient cases. Coughing, he says, will often cause signs of cavity to become more marked; gurgling râles originating in the cavity may also aid in the diagnosis. Norris believes that cavities are more frequently overlooked than erroneously diagnosed when absent. All wise statements are true if applied to a certain group of cases; but they cannot be expected to hold true for all cases.

Mantoux[7] believes that in tuberculous patients the clinical diagnosis should be made certain and confirmed by bacteriologic and roentgenologic examination. The three methods, he says, are equally indispensible; one corrects the error of the other. An examination of a tuberculous patient is incomplete if it does not rest on this diagnostic triad.

Fishberg[8] concludes by saying, "On the whole, cavities indicate chronicity of the tuberculous process in the lung." "It shows," he says, "that the resisting forces are active." From my experience in this institution I am of the opinion that such conclusions are erroneous (Tables 1, 2, 3 and 4).

Allyn[2] regards the following signs as most trustworthy in diagnosing a tuberculous cavity in the lung; deficient expansion or flattening of the chest wall over the cavity on breathing; high pitched tympany on percussion, especially if percussion is made with the mouth open; whispered pectoriloquy; cavernous breathing; multiplicity of râles, particularly moist râles which, after coughing, have a resonating quality. Rieder[4] points out the danger of infection of one part from cavities in another part of the lung.

Ribadeau-Dumas[15] concludes that clinical methods are insufficient. In eleven cases of tuberculosis with cavities the size of a large nut, but few were suspected during life.

Lhomme[19] believes that functional and physical signs of cavity are deceptive and that the diagnosis of cavities in infants is difficult.

Pallasse and Roubier[12] and Bernand and Tecon[13] point out that other diseases, such as dilatation of bronchi, pulmonary syphilis, post-pneumonic abscess, encysted pleurisy, partial pneumothorax, or gangrene, may be confused with tuberculous cavity signs.

I have already called attention in our cases to other conditions which have been diagnosed as cavities and others in which cavities were present, the physical signs being absent.

In order to establish the diagnosis of cavity by physical means, the presence of certain sounds and signs is necessary. The study of the skeletal and muscular asymmetry of the thorax is helpful—the demon-

TABLE 5.—Physical Signs in Cavity Area

Whispered Pectoriloquy	Bronchovesicular Breathing	Bronchial Breathing	Feeble Breathing	Amphoric Breathing Sounds	Tinkling	Râles	Dullness	Diminished Resonance	Harsh Resonance	
+	..	..	..	..	..	+	+	..	..	6 D
..	+	+	..	?+	..	+	+	..	..	7 H
+	+	+	..	..	..	+	+	+	..	46 G
+	+	..	..	..	..	+	+	..	..	71 A
+	..	+	..	..	..	+	+	..	..	70 F
+	+	..	..	..	..	+	..	+	..	90 B
+	+	..	..	..	..	+	+	..	..	123 S
+	..	+	..	..	..	+	+	..	..	127 M
+	+	..	..	..	..	+	..	+	..	125 S
+	+	..	..	..	..	+	..	+	..	128 G
+	+	+	..	..	..	.	+	..	..	150 G
+	+	+	..	..	..	+	+	..	..	170 F
+	+	..	..	..	..	+	+	..	..	178 S
+	..	+	..	..	..	+	+	+	..	204 T
..	+	..	..	..	..	+	+	..	..	225 U
..	..	+	..	..	..	+	+	..	..	227 C
..	+	..	..	..	..	+	+	..	..	228 C
..	..	+	..	..	..	+	+	..	..	237 G
+	+	+	..	..	..	+	..	+	..	238 Y
+	..	+	..	..	..	..	..	..	+	396 H
+	+	..	..	..	+	+	+	..	..	408 C
..	+	..	..	..	..	+	+	+	+	442 W
+	+	..	+	..	..	+	+	..	..	443 S
+	+	..	..	..	..	+	+	..	..	466 U
+	+	..	..	..	..	+	..	+	..	487 H
+	..	+	..	..	..	+	..	..	..	543 L
..	+	..	..	..	..	+	..	+	..	546 E
+	+	..	+	+	..	+	..	..	..	586 S
+	+	..	..	.	+	+	..	+	..	601 M
..	+	..	+	+	..	+	+	..	..	602 W
..	+	..	..	..	..	+	..	+	..	645 H
..	+	..	..	..	..	+	..	+	..	646 A
+	+	..	..	+	+	+	+	..	..	652 K
..	+	..	..	..	..	+	+	+	..	669 F
+	+	..	..	..	..	+	..	+	..	656 G
..	+	..	..	..	..	+	+	..	..	688 D
+	+	..	..	..	..	+	+	..	..	732 S
+	+	..	..	..	..	+	+	..	..	766 D
+	+	..	..	..	..	+	+	..	..	769 F
+	..	+	..	..	..	+	..	..	..	810 S
..	+	..	..	..	..	+	+	..	..	848 T
..	..	..	..	..	..	..	..	..	+	930 D
+	+	..	..	..	..	..	+	+	..	858 M
..	+	..	..	..	..	+	..	..	..	936 L
..	+	..	+	..	..	+	+	+	..	951 G

TABLE 6.—Summary of Table 5, Showing the Physical Signs in the Cavity Area in Forty-Five Cases

	Number of Cases	Percentage of Cases
Whispered pectoriliquy	25	55
Bronchial vesicular breathing	35	77
Bronchial breathing	14	31
Feeble breath sounds	4	8
Amphoric breathing	3+ ?1	8
Tinkling	3	6
Râles	42	93
Dullness	28	62
Diminished resonance	16	35
Harsh resonance	3	6

TABLE 7.—POSTMORTEM FINDINGS AND ROENTGENOGRAPHIC FINDINGS COMPARED *

No.	Position	Postmortem Findings	Position	Roentgen Findings
7H	Left	A large cavity, upper lung, anteriorly, medially, and posteriorly	Left	1st rib, circular cavity, 5½ × 5½ cm.
	Right	Smaller cavities, middle of lung, medially		
71A	Right	A large cavity, upper lobe, anteriorly, laterally and medially	L & R	Apices, indefinite cavities of indefinite size
123S	Left	A large cavity, upper lung, anteriorly, medially and posteriorly	Left	3d to 1st rib, irregular oval capacity, 5 × 5 cm.
	Right	Smaller cavities, middle lung, anteriorly, medially and posteriorly		
128G	Left	A large cavity, upper lung, anteriorly, medially and posteriorly	Left	1st to 3d rib, irregular oval cavity, 3½ × 3 cm.
150E	Right	A large multilocular cavity, upper lung, anteriorly and medially; a smaller cavity, lower lung, posteriorly	Left	1st rib up, irregular cavities, 3 cm.+
	Left	An enormous cavity occupying the upper third of the lung	Right	3d rib up, multiple cavities
178S	R & L	Multiple cavities, upper lung, anteriorly	Left	Apex, circular cavity, 6 × 6 cm.
225U	Right	A large cavity, upper lung, anteriorly, medially and posteriorly, 6 cm. in diameter; 2 smaller cavities situated near the hilus of the lung, approximately 2 cm. in diameter	L & R	Several cavities, 1st and 2d spaces; circular; 6 × 2 × 1½, right; 1 × 1½ × 2, left
226C	Right	A large cavity, 8 cm. in diameter, upper lung, anteriorly, posteriorly, and laterally; many smaller cavities below	Right	Multiple circular and oval cavities, 1st, 2d, 3d spaces, 2 × 3 cm.+
227C	Left	A large cavity and many smaller ones, upper lung, anteriorly, posteriorly laterally	Left	2d rib up, indefinite cavity, 5+ cm.
	Right	Many large cavities, upper lobe, posteriorly, anteriorly, laterally and medially	Right	Over 1st rib, circular cavity, 3 × 3 cm.
442W	Left	A multilocular cavity, upper lung, anteriorly, posteriorly and medially	L & R	Multiple circular and irregular cavities, 3d rib up, 3 cm.+
	Right	A cavity in the upper lobe anteriorly and lower anterior portion; several small cavities in mid portion; small cavity in mid portion of lower lobe		
443E	Left	A large cavity and smaller cavities throughout upper half of lung, medially	Left	2d space, irregular circular cavity, 3 × 3½ cm.
487H	Left	Lung collapsed	Left	Cavity; pneumothorax
	Right	Many small cavities throughout	Right	1st and 2d ribs, circular and oval cavities, 5 × 4 × 3 × 4 cm.
546E	Left	Two large cavities, upper lung, medially	L & R	1st and 2d space, oblong cavities 2 × 1½ cm.
	Right	Smaller cavities, upper lung, medially		
601M	Right	A large cavity, upper lung, anteriorly, medially and posteriorly; smaller cavities, middle and lower lung, anteriorly	Right	Upper and middle, irregular oval cavities, 2 cm.+ and 6× 6 cm.
	Left	Smaller cavities, upper lung, anteriorly, medially and posteriorly		
602W	R & L	Small cavities, upper lung, medially	R & L	Upper lobes, oval cavities, 6 × 6 and 6 × 4 cm.
645H	R & L	Large cavities and multiple smaller ones, upper lung, anteriorly, medially and posteriorly	L & R	1st rib, oval and circular cavities, 6 × 4, right; 6 × 4, left
646A	Right	A large cavity, upper lung, anteriorly, medially and posteriorly	Right	Middle and lower, indefinite and circular cavities, 2 cm.+ and 3 × 2 cm.
	Left	Smaller cavities, upper lung, anteriorly, medially and posteriorly		

TABLE 7.—Postmortem Findings and Roentgenographic Findings Compared*—(*Continued*)

No.	Position	Postmortem Findings	Position	Roentgen Findings
652K	Left	Many small cavities, upper lung	Right	1st space, circular cavity, 5 × 4 cm.
	Right	A large cavity, apex, anteriorly, medially and posteriorly, 6 × 6 cm. in diameter	Left	Multiple, 3d rib up
688D	Left	A large cavity, upper and middle lung, anteriorly, medially and posteriorly	Left	Multiple, apex, 2d rib up, indefinite in size and shape
	Right	A large cavity, middle lung, anteriorly, medially and posteriorly; small cavities, lower lung, medially		
732S	Left	Large cavities, anteriorly, medially and posteriorly, upper lung; multiple smaller cavities throughout outer portion, posteriorly	L & R	Upper lobes, many oval and circular; right, 6 × 7; left, 3 × 1¼ to 5 × 3 cm.
	Right	Large cavities, upper lung, anteriorly, medially and posteriorly		
766D	Left	A large cavity, upper lung, anteriorly, medially and posteriorly; smaller cavities, middle and lower lung, medially and posteriorly	Left	Multiple, 3d rib up, indefinite shape, 2+ cm. in diameter
769F	Left	The whole lung, except a small area in the lower posterior is one large cavity	Right	All lobes, circular and oval cavities, 3 cm.+
	Right	A large cavity, 6 × 8 cm. in diameter, apex, anteriorly, medially and posteriorly	Left	2d rib up
810S	Left	Large cavities, upper lung, anteriorly, medially and posteriorly; multiple smaller cavities throughout middle lung, medially and posteriorly	L & R	Multiple circular and oval cavities, 3d rib up, 3 cm.+
	Right	Large cavities, upper lung, anteriorly, medially and posteriorly		
930D	Left	A multiloecular cavity, upper third; numerous small cavities in midportion, anteriorly, medially and posteriorly	Left	3d rib up, multiple indefinite cavities
	Right	Smaller cavities, upper lobe	Right	Over 2d rib, multiple indefinite cavities
951G	Right	A large cavity, upper lung, anteriorly and posteriorly	Right	5th rib up, multiple circular cavities, 4 cm.+
1002T	Left	Numerous small cavities throughout	Right	4th rib up, multiple indefinite cavities
237D	Left	Numerous small cavities, upper lobe, varying in size from 1 to 8 cm.; lower lobe, upper portion, several cavities of not more than 15 mm.	Left	Several small circular cavities, 1 cm. and more

* The postmortem findings as compared with the roentgenographic findings, in fourteen of the twenty-seven cases coming to necropsy showed that the position of the cavities was correctly diagnosed by roentgenograph, or 51 per cent.; in ten cases, or 37 per cent., the position of some of the cavities was correctly diagnosed by roentgenogram, and in only three cases, or 11 per cent., was the roentgenographic diagnosis shown by necropsy to be incorrect.

stration of fixation or immobilization of a local area (say, for instance, the right upper portion from the third rib front) is important. An absence of movement in this area, or lagging in breathing, and an appearance of collapse in contrast to compensatory changes on the opposite side (that is, greater size, extension, more respiratory movement, greater filling and expansion), is of first consideration.

Consequently, by inspection and measurement much information can be obtained to aid in the more detailed diagnosis obtained by auscultation and percussion. The extent of the tuberculosis should be

determined first; the degree of apical involvement as compared with that at the base; whether there is hilus involvement; whether the pleura is affected, and to what extent, if any, the movements of the diaphragm are diminished.

The duration of the disease, the chronicity of the process and the course of the infection are of assistance in diagnosing cavity. However, the lung should be in such a condition as regards the cavity that signs or combinations of sounds and conditions can be elicited and heard sufficiently clearly, intensely and constantly to be considered as diagnostic of cavity. The same rule holds good clinically regarding size, position, etc., of cavity as obtained roentgenologically.

In the patients examined at U. S. Army Hospital No. 16 during the period of one year, 449 were definitely diagnosed as having tuberculosis of one or more lobes. We are, therefore, concerned with these cases, for among this number there occurred seventy-four cases of cavitation (Table 1). In the examination of the patients with cavitation the physical signs detailed in Tables 5 and 6 were found. Consequently, an analysis of the figures given here will aid in appreciating the subject as a whole.

RAT BITE FEVER*

REPORT OF A CASE

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DEFINITION

Rat bite fever (Sodoku of the Japanese; Rattenbisskrankheit; toxi-infection par morsure de rat; morbo da morso di topo, etc.) is an acute infectious disease caused by *Spirochaeta morsus muris*, following the bite of the rat (rarely cat, weasel, ferret or other animal) and characterized, after an incubation period, by recurring paroxysms of fever, a blue red exanthem, marked nervous symptoms, emaciation and weakness.

HISTORICAL

The disease is best known in Japan where it has long been endemic. For a review of the history of this extremely interesting and rare disease the reader is referred to the excellent report of the disease in Japan by Miyake,[1] who, in 1900, found no cases recorded in the European literature. In the older Japanese literature appear many references to a disease incident on the bite of the rat, but not fully described. The first good description in modern Japanese publications appeared in 1890, in Katsura's system of surgery.

Not only was the disease recognized early as being related to the bite of the rat in Japan, but it appeared also in the settlement days in our own country. Several reports of an unusual febrile disease, accompanied by severe nervous symptoms, and following the bite of the rat are found in our early medical journals. Of these, perhaps, the first is that of Dr. Whitman Wilcox[2] published in 1840. Reporting an attack following the bite of a rat he states: "Very little notice was taken of the wound until 12 or 13 days afterwards, when it commenced to be painful and tumefied. I was called in on the evening of the 17th, and found him with pain in the back and head, heat of skin, thirst, tongue with a thin white coat, bowels costive, hand painful and swollen, pulse nearly natural, etc." He then describes severe mental symptoms, gangrene of the wound, with sloughing of the skin. He also mentions a relapse occurring three or four days after subsidence of the first

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* From the Department of Pathology and Bacteriology of West Virginia University School of Medicine.

1. Miyake, H.: Ueber die Rattenbisskrankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **5**:231, 1899.

2. Wilcox, W.: Violent Symptoms from the Bite of a Rat, Am. J. Med. Sc. **26**:245, 1840.

attack and lasting five to six days. This description corresponds closely with our present conception of rat bite fever. The characteristic exanthem and the lymphangitis and adenitis were not mentioned, however; nor was the relapsing type of fever carefully described.

In a study of the French literature, Roger[3] has found an excellent report of the disease made by Millot-Carpentier[4] in 1884, which leaves little doubt that his report of the disease was the first in Europe, and preceded the Japanese study of Miyake. In 1909, Horder[5] reported three cases from England. Crohn[6] in this country, reviewing the literature in 1915, found a total of fifty-two cases, and added one case which he reported. Blake,[7] in 1916, collecting the cases reported at that time, found a total of eighty-one on record in the entire literature.

I have found forty-eight cases reported since 1916 to July, 1919. These reports are given in the list of references. This makes the cases to date, including the eighty-one collected by Blake to 1916, number about 130.

INCIDENCE OF DISEASE

Cases have now been reported from Japan, France, England, the United States, India, Italy, Morocco, Scotland, China, Spain, Germany, Brazil, Australia and the Philippines. It is interestitng to note that medical officers of the army have reported a number of cases among soldiers in the trenches in France and elsewhere. The similarity of the fever to trench fever, and the presence of obscure fevers, makes it necessary to keep this disease in mind in the trenches. A failure to obtain the history of a rat bite, or to recognize the cardinal symptoms of rat bite fever, might more easily occur among soldiers in active warfare.

The greater prevalence of the disease in Japan is probably due to the fact that more people live in wooden houses, where rats are numerous. Whether the percentage of infected rats is higher in Japan than in other countries cannot be known until a study of the prevalence of the spirochete in rats in different countries is made. According to Japanese investigators, the organism is found in from 3 to 12 per cent.

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3. Roger, H.: Erytheme toxi-infectieux et septicemie legere par morsure de rat des tranchees; un cas de sodoku fruste, Marseille méd. **53**:321, 1916. Le cas français de sodoku; toxi-infection par morsure de rat, Presse méd. **25**: 201, 1917. De l'anciennete, en France, de la toxi-infection par morsure de rat (sodoku des Japonais), Rev. gen de clin. et de therap., Par. **31**:323, 1917.

4. Millot-Carpentier: Considerations medico-physiologiques sur un cas de morsure de rat suivie d'intoxication ayant determine des accidents nerveux simulant l'hydrophobie et l'apparition d'un purpura a forme intermittente. L'Union méd., Par. **38**:1069, 1884.

5. Horder, T. J.: Rat Bite Fever, Quart. J. Med. **3**:121, 1909.

6. Crohn, B. B.: Rat Bite Fever, Arch. Int. Med. **15**:1014, 1915; also Ref. Handb. M. Sc., New York **7**:483, 1917.

7. Blake, F. J.: The Etiology of Rat Bite Fever, J. Exper. Med. **23**:39, 1916.

of rats in that country. It is possible that the disease has been carried from Japan to other countries by infected rats. A study of infection in rats in different countries may help to determine this.

PREDISPOSING CAUSES

Age and sex seem to play no part in the occurrence of the disease. It has been found at various ages and in either sex. Occupation is important only in so far as it renders the person more liable to be bitten by rats. Hence more cases have been found among farmers, seamen, and soldiers in the trenches. Previous illnesses have no relationship to infection. Not all persons bitten by rats develop rat bite fever. There are a number of determining factors, such as (1) infection of the rat; (2) location of the wound—a wound on the exposed parts of the body is more likely to become infected than one through clothing, just as in rabies; (3) depth of the wound—in some cases a scratch has sufficed, in others free bleeding may cleanse the wound of infection; (4) mixed infection, which may inhibit growth of the spirochete or aid it. Cases have been reported of several persons bitten by the same rat, one developing the disease, another showing no symptoms (Miyake[1]).

THE CAUSE OF RAT BITE FEVER

Since the recognition of rat bite fever as a distinct disease, several reports of the discovery of a micro-organism associated with the malady have been published. The following may be mentioned: (1) Streptothrix, Schottmüller,[8] Blake, Tunnicliff,[9] Litterer,[10] Tileston.[11] (2) Sporozoon, Ogata.[12] (3) Telosporidia, Shikami. (4) Diplococcus, Middleton; Douglas, Colebrook and Fleming.[13] (5) Spirochaeta morsus muris, Futaki and associates[14] Ishiwara and associates,[15] Ido and

8. Schottmüller, H.: Zur Aetiologie und Klinik der Bisskrankheit, Dermat. Wchnschr. **58**:77, 1914.

9. Tunnicliff, R.: Streptothrix in Bronchopneumonia of Rats Similar to That in Rat Bite Fever. Preliminary Report, J. A. M. A. **66**:1606 (March 25) 1916; J. Infect. Dis. **19**:767, 1916. Tunnicliff, R. ,and Mayer, K. M.: A Case of Rat Bite Fever, J. Infect. Dis. **23**:555, 1918.

10. Litterer, W.: New Species of Streptothrix Isolated from a Case of Rat Bite Fever, J. Tennessee M. A. **10**:310, 1917.

11. Tileston, W.: The Etiology and Treatment of Rat Bite Fever, J. A. M. A. **66**:995 (March 25) 1916.

12. Ogata, M.: Die Aetiologie der Rattenbisskrankheit, Deutsch. med. Wchnschr. **34**:1099, 1908; Mitt. a. d. med. Fakult. d. k. Univ. z. Tokyo **8**:287, 1909; **9**:343, 1911; **11**:179, 1913.

13. Douglas, S. R., Colebrook, L., and Fleming, A.: A Case of Rat Bite Fever, Lancet **1**:253, 1918.

14. Futaki, K., Takaki, I., Taniguchi, T., and Osumi, S.: The Cause of Rat Bite Fever, J. Exper. M. **23**:249, 1916. Spirocheta morsus muris, n. sp., the Cause of Rat Bite Fever, J. Exper. M. **25**:33, 1917.

15. Ishiwara, K., Ohtawara, T., and Tamura, K.: Experimental Rat Bite Fever. First Report, J. Exper. M. **25**:45, 1917.

associates,[16] Kitagawa and Mukoyama,[17] Kaneko and Okuda,[18] Kusama and associates,[19] etc.

That the bite of an animal, especially the rat, may cause infection in man with different micro-organisms is obvious to anyone who makes a careful survey of the literature of diseases produced by animal bites (rat, cat, ferret, weasel, dog, mouse, etc.). This is not at all surprising in view of the demonstration in rats of many parasites (streptothrix in bronchopneumonia of rats by Tunnicliff; *Spirochaeta icterohemorrhagiae* in rats by Ido in Japan; Noguchi,[20] Jobling and Eggstein in America, and a number of investigators in Europe; *Spirochaeta morsus muris*, Futaki and associates, Kusama and associates, Coles;[21] *Spirillum minor* Carter, *Spirochaeta laverani* Breinl and Kinghorn, *Spirochaeta muris* Wenyon, which three may be similar to *Spirochaeta morsus muris* Futaki; spirochetes of Borrel, Calkins, Mezinescu, etc. Still others may be present in the saliva of the rat, such as pathogenic streptococci, virus of rabies, etc.). Mixed infections with more than one organism might, therefore, occur.

From a study of the disease I am of the opinion that rat bite fever is caused by a specific micro-organism first observed by Futaki and his associates, *Spirochaeta morsus muris*, for the following reasons: (1) The disease is a definite clinical entity, as will be described later. (2) *Spirochaeta morsus muris* has been found in the blood and tissues of persons suffering from the disease, in the wild rat and field vole, all three strains belonging to the same species. (3) The disease has been produced in animals by the bite of inoculated rats and pure cultures, and the spirochete found. (4) Specific immune bodies, spirocheticidal and spirochetolytic) are present in the blood of patients. (5) Arsphenamin has a specific therapeutic action in the disease.

There are several difficulties in the way of demonstrating the specific organism in rat bite fever, and it is to aid in overcoming these

16. Ido, Y., Hoki, R., Ito, H., and Wani, H.: The Rat as a Carrier of Spirochaetosis Icterohemorrhagiae, the Causative Agent of Weil's Disease (Spirochaetosis Icterohemorrhagica), J. Exper. M. **26**:341, 1917.

17. Kitagawa, J., and Mukoyama, T.: The Etiologic Agent of Rat Bite Disease. Preliminary Report, Arch. Int. Med. **20**:317 (Sept.) 1917. Kitagawa, J.: Clinical Experience with Cat Bite Disease, Saikingaku Zasshi, No. 260, p. 422, 1917; abstr. in China M. J. **33**:55, 1918.

18. Kaneko, R., and Ōkuda, K.: A Contribution to the Etiology and Pathology of Rat Bite Fever, J. Exper. M. **26**:363, 1917.

19. Kusama, S., Kobayashi, R., and Kasai, K.: The Rat Bite Fever Spirochete, with Comparative Study of Human, Wild Rat and Field Vole Strains, J. Infect. Dis. **24**:366, 1919.

20. Noguchi, H.: Spirochaeta Icterohemorrhagiae in American Wild Rats, and Its Relation to the Japanese and European Strains, J. Exper. M. **25**: 755, 1917.

21. Coles, A. C.: Rat Bite Fever, Lancet **1**:350, 1918.

that I wish to summarize our present knowledge of the disease. First, the rat that produces the bite is not obtained for examination. I have not been able to find a single report of such an examinatiton. Not infrequently the rat is caught and killed, but there is a failure by the physician or patient, or both, to recognize its relation to the disease. Second, the spirochete is present in the blood, skin lesions and lymph glands in greatest number at the height of the first few febrile attacks, when smears and animal inoculations should be made. In some cases it may be absent from the blood, or there may be so few as to be overlooked. This will be discussed under diagnosis.

MODE OF INFECTION

The spirochete is inoculated in the tissues with the bite. It is present in the mouth of the rat probably from abrasions of the mucous membrane of the gums, as spirochetes have not been found in the mouths of experimentally inoculated rats, even when they have been able to produce the disease in other animals by a bite and when spirochetes have been present in the blood. Abrasions of the gums could easily occur. The germ has been found in the submucosa of the gums and also in the salivary glands of inoculated rats. It is present in the blood of these rats in considerable number about the eighth day after inoculation, also in the kidney and suprarenals.

Rats may also become infected by preying on infected rats and then transmit the disease by biting man or lower animals.

SPIROCHAETA MORSUS MURIS

This organism was first discovered by Futaki, Takaki, Taniguchi and Osumi in 1915. These investigators found a spirochete in the skin lesions, local lymph glands and blood of two of four cases. In the study of six other cases the following year they found the spirochete in five; in two of these it was found in the blood. Two types of spirochete were found, one, a short form, in the blood, the other a long form, in the tissues. Ishiwara and Ohtawara found a similar spirochete in animals infected by the bite of rats, confirming the findings of Ogata on infection by rat bite. In 1916, Futaki found that the two types are probably the same spirochete, intermediate forms also occurring. Kaneko and Okuda came to the same conclusion from the study of the pathologic anatomy of human cases in which they found the spirochete. Kitagawa and Mukoyama were able to infect rats, guineapigs and monkeys with an axillary lymph gland from a patient and found the same spirochete. Row[22] has observed a spirochete in rat

22. Row, R.: On a New Species of Spirochete Isolated from a Case of Rat Bite Fever in Bombay, Indian J. M. Res. **5**:386, 1917.

bite fever in Bombay. Sano,[23] and Costa and Troisier[24] have also found a spirochete in this disease. The organism has not yet been seen in cases in this country.

The spirochete varies in length from 2 to 6 microns, with its flagella it is from 6 to 10 microns long. The short form is usually found in the blood of patients and in experimental animals, and is probably the young form. The long form is found chiefly in human tissues, and in culture mediums. Intermediate forms and degenerating forms also appear. In cultures the organism is from 1.5 to 19 microns in length, thicker than the *Spirochaeta pallida*, and possesses one curve per micron. The curves are regular and sharp. There are usually from one and one-half to six curves, occasionally as many as nineteen. It stains readily with Giemsa's stain, also with Loeffler's methylene blue and gentian violet. It is gram-negative. Burri's india ink method is very satisfactory. Levaditi's method is best for staining the organism in tissues.

The organism is motile, having a rapid movement. Cultivated ones are less active. Infection occurs in the mouse, wild rat, guinea-pig and monkey. The guinea-pig and monkey develop the characteristic fever and other symptoms, whereas the other animals present the spirochete in great number in the peripheral blood without definite symptoms. In the mouse spirochetes appear in the blood in from five to fourteen days after inoculation, and the animal usually survives. Mouse inoculation is a valuable aid in isolating the spirochete. In the guinea-pig the infection usually results fatally with swelling and congestion of the bitten part, enlargement of lymph nodes, fever, loss of weight and alopecia. Acute inflammatory changes are found in the kidney, and hyperemia and hemorrhages occur in the suprarenal where spirochetes are usually most numerous. Hyperemia of the lungs and catarrhal inflammation of the gastric mucosa also occur. In the monkey the symptoms are very similar to those in man and the infection is often fatal. However, a monkey recovered from the infection shows no symptoms on reinoculation.

In a very recent study by Kusama, Kobayashi and Kasai, which shows the human, wild rat and field vole strains of spirochete to be the same, the authors find that on inoculation of a rat or guinea-pig the spirochete for the first two weeks is found chiefly in the blood. Then it appears in the connective tissues of various parts of the body

23. Sano, T.: Rat Bite Disease. Case Report, Iji Shimbun, No. 981, p. 1153, 1917; abstr. China M. J. **32**:469, 1918.

24. Costa, S., and Troisier, J.: Un cas de sodoku (fievre par morsure de rat), Bull. soc. med. de hôp de Par. **40**:1931, 1916. Un nouveau cas de sodoku. Spirochetes a l'examen direct du sang, Bull. et mem. Soc. med. de hôp. de Par. **42**:616, 1918.

(submucosa of eyelids, lips, nose and tongue; capsule of lymph glands and salivary glands; adventitia of large blood vessels; parenchymatous organs). None are present in the normal saliva, intestinal contents or bile. They may appear in the urine.

That a streptothrix may be found in cases of rat bite fever was first demonstrated by Schottmüller, and later observed also by Blake, Tileston, Tunnicliff and Litterer. The fact that in some of these cases arsphenamin was used with prompt cure makes it very likely that the streptothrix was not the specific cause, but only a secondary invader. Recognizing the difficulties in finding the spirochete in blood smears, and also in obtaining positive animal inoculations when the blood and tissues are examined late in the disease or between paroxysms of fever, sometimes even during the attacks, one is not surprised at failure to find the spirochete in most cases of rat bite fever. Also the ulcerative endocarditis, and degenerative and infiltrative changes found in the organs in Blake's fatal cases are not demonstrable in experimental rat bite fever in animals, and have not been found in the other necropsies done on rat bite fever victims. I think that the specific action of arsphenamin, as found by Tileston, rules out the streptothrix as the cause of the disease in his cases.

SYMPTOMS

A. The Bite.—The bite is usually a small punctiform area which heals readily in a few days, the time depending on its size. It usually does not suppurate. In some cases, however, necrosis of the skin and subcutaneous tissue with sloughing, followed by slight pigmentation, occurs. Pus formation is due to secondary infection.

B. Incubation Period.—The average length of the incubation period is twelve days; it varies from five to thirty days. A few cases have been reported with symptoms manifested in less than five days, and some months after the bite. The latter cases were not controlled carefully, and probably were incorrect. In severe and prolonged cases, which seem to be more common after bites on the face or head, the incubation period is usually shorter than the average.

C. Prodromata.—As a rule, within two weeks after the bite the patient complains of pain and heat in the bitten area, which is swollen, of a bluish red color and somewhat indurated. The pain may become severe, being sharp or pulsating.

About the area of acute hyperemia may be a slight edema of the skin, giving a ring-like appearance about the central bluish red induration. Sometimes the bite resembles closely an extra-genital primary lesion of syphilis. Reddish streaks appear in the direction of the local lymph glands, which soon become enlarged, tender, hard, but discrete.

The patient begins to complain of headache, pains in the muscles of the back and extremities and malaise. Soon the most constant symptom, the fever, appears.

D. Fever.—With the prodromal symptoms, inflammation of the bitten area, and lymphangitis and adenitis there usually occurs a sudden rise of temperature, from 102 to 105 F. It is ushered in with severe chills, great pains in the limbs, and headache. The pulse is rapid, full and soft. The patient often complains of great thirst, nausea and vomiting and a feeling of anxiety. The skin is pale, and the extremities are cold. In severe cases hallucinations, and even delirium or coma may accompany a fatal outcome during the first paroxysm of fever. The paroxysm usually lasts from three to six days, when it falls by crisis with profuse perspiration and great improvement in the condition of the patient.

After an apyrexia of from two to six days another attack occurs. In fatal cases the attacks may become more severe until death results. As a rule, subsequent attacks become less severe and less frequent until in a few months they disappear. The average duration of the disease is two months. However, Kitagawa and Mukoyama have seen a case with recurrences fifteen years after the first attacks, and Kusunoki states that one or two relapses per year occur for ten years after recovery from rat bite fever. The patients treated with arsphenamin seem to be entirely free from recurrences.

The fever not infrequently shows irregularity. At first it may be continuous or remittent. Later the attacks are of shorter duration and do not reach as high. On account of the variability of the fever, the cases may be classified into the following types:

1. Febrile form with exanthem:
   (a) Intermittent fever.
   (b) Continuous fever.
2. Febrile form with nervous symptoms:
   (a) Acute.
   (b) Subacute.
3. Afebrile form with marked nervous symptoms.
4. Abortive form.

The paroxysms may vary from one severe fatal attack, or one mild prolonged attack with continuous fever for as long as twenty days, to as many as thirty attacks. The average is about from five to ten attacks. They occur at least once a week at first. As already mentioned, they last from three to six days, to a day or less later in the course of the disease. The interval also varies somewhat, averaging four days.

E. Nervous Symptoms.—Involvement of the nervous system occurs in most cases of rat bite fever. There is usually severe headache, dizziness, ringing in the ears, blurring of vision, especially during the paroxysmal attacks of fever. In the acute cases delirium or coma may develop. Hemicrania, neuralgic pains and especially pains in the muscles of the extremities, mostly in the lower, occur. Beginning with the first or second attack of fever the pain may be generalized, and later remain localized in the lower extremities. In some cases persistent neuralgic pains have been recorded for months or years.

Motor disturbances may develop in the form of paresis of the lower extremities, rarely the upper, and they may become very marked. This usually disappears with recovery from the fever. The tendon reflexes may be exaggerated, less often abolished. Progressive atrophy of the extremities has been reported.

Sensory changes occur in most severe cases, from paresthesias to complete anesthesia in some areas, mostly the extremities. These usually last through the febrile period. Hyperesthetic or hypoesthetic zones may be found in different parts of the body.

The febrile type, with acute nervous symptoms, is suggestive of the symptoms of rabies. The patient complains of severe pain in the bite, dizziness, great anxiety, headache. Dyspnea, rapid and small pulse, sensory and motor disturbances of the extremities, collapse, delirium or coma and even death may follow.

There is also a subacute form. After the incubation period, with or without any exanthem, the patient complains of severe, persistent, muscular pains; there may be paralysis of the lower extremities, with loss of patellar reflexes. The motor and sensory disturbances may be of long duration.

In the abortive type the patient may have only a few mild attacks of fever; the exanthem may be confined to the region of the bite, or it may be entirely absent. There are vague general symptoms, malaise, headache, slight weakness. Recovery is rapid, usually in a week or two.

F. Skin Manifestations.—The exanthem is rarely absent, as in the mild or abortive cases. It usually makes its appearance with the first attack of fever and lasts several days, when it may disappear, leaving a slight pigmentation or desquamation. With the recurrence of the fever the exanthem usually reappears, or new eruptions become visible. Sometimes the rash is not visible until the second, third or later attack of fever.

It may affect the skin about the bite, or an extremitiy, or more frequently it appears on the face, neck, back, chest, abdomen and extremities and less often in the palms of the hands and on the soles of the feet. A rash on the mucosa of the mouth has also been

described. The rash is not symmetrical. It begins as a macular eruption, red to blue red in color, varying in size from 5 mm. to 10 cm., usually round or oval and well defined. Later the spots become elevated; the center may be higher than the periphery and paler in color. The color does not entirely disappear on pressure or only on deep pressure, which causes some pain. The areas are slightly indurated.

In cases where the rash is localized near the bite or on the extremity, large, bluish red, elevated, indurated areas appear, from a dime to the palm of the hand in size. They often are distributed along the course of the lymphatics and over the enlarged lymph glands. They are slightly painful on pressure.

Miyake has described an acute urticaria, which he states is very characteristic of the disease toward the end of its course. It is spread over the entire body, often accompanied by fever. It may be overlooked unless the patient is kept under observation until recovery is complete.

G. Lymphatics.—That the spirochete infection spreads at first by the lymphatics is indicated by the frequent occurrence of lymphangitis. Reddish streaks are seen extending from the bite to the lymph nodes of the area. These appear just before the first attack of fever and usually disappear entirely in a few days. Then the local lymph glands become enlarged, sometimes reaching the size of a hen's egg, though usually smaller than this. After the first three or four attacks of fever the glands return almost to normal; in some cases they remain large throughout the disease, enlarging and becoming painful with each attack of fever.

The glands do not suppurate. They are elastic, rather soft, and later become harder. There is pain on pressure, and often considerable tenderness. The enlargement is usually confined to the regional glands, though the others may also become affected.

H. Gastro-Intestinal Tract.—The gastro-intestinal symptoms are not severe. A white coated tongue, nausea and vomiting are not uncommon. Constipation is more often present than diarrhea. In a few cases severe dysphagia, almost resembling that of rabies, has been reported. The appetite is usually poor during the acute attacks, but may return to normal between the paroxysms.

The liver and spleen are not, as a rule, enlarged.

I. Genito-Urinary Tract.—Evidence of nephritis is found in about 10 per cent. of the cases. It may vary from an acute fatal parenchymatous nephritis to a mild attack. In the severe form there is a reduction in the urinary excretion, albumen, casts and some red cells are present in the urine. In other cases there is only a slight amount of albumen with few casts. That the spirochete has a tendency to attack

the kidney is also shown by its presence there in large number in experimental animals after inoculation.

J. Circulation.—The pulse usually varies with the height of the fever. It is rapid and small. There may be evidence of myocardial weakness, probably due to the toxemia as well as the secondary anemia. In severe cases there may be palpitation of the heart, and a hemic murmur is often heard at the apex.

K. Respiratory Tract.—The respiratory system is little affected. Slight bronchitis may develop. In prolonged and fatal cases terminal pneumonia may occur. The dyspnea in severe cases develops with the high fever, and may be toxic in origin.

PATHOLOGY

Little is known of the pathologic anatomy of this interesting disease. Miura[25] examined one case seventeen hours postmortem, and found only an increase in the amount of cerebrospinal fluid and hyperemia of the pia mater. There were no specific changes in the internal organs. Histologic examinations were not made. Blake's case was a streptothrix septicemia, with localization of the streptothrix in the mitral valve, producing an acute endocarditis followed by infarct formation in kidney and spleen. Subacute lesions of the parenchymatous organs also were present. These degenerative and infiltrative changes have not been observed in experimental rat bite fever, nor in other postmortems in human cases, hence we are forced to conclude that they do not represent the picture of true uncomplicated rat bite fever.

In 1917 Kaneko and Okuda reported the findings in two cases. There were parenchymatous changes in the organs. In the kidney occurred hyperemia, swelling and degeneration of tubular epithelium. They report the presence of spirochetes in the kidney, in the cortex of the suprarenal and in the interstitial cells of testis. The liver presented fatty degeneration, necrosis chiefly in the centers of the lobules, hyperemia and hemorrhage. The local lymph nodes were hyperemic, with an inflammatory cellular hyperplasia, hemorrhages and erythrophagocytosis. Other lymph glands were swollen and hyperemic. Catarrhal changes in the mucosa of the stomach and urinary bladder, congestion of the lungs, and hyperemia and edema of the meninges occurred. Slight degeneration of muscle and nerve cells was found. At the site of the bite cellular infiltration, edema and degeneration (acute exudative inflammation) appear. There is frequently a lymphangitis extending from the bitten area to the lymph glands, shown by the presence of reddish streaks along the course of the lymph channels. This is followed by the lymphadenitis already mentioned.

25. Miura and Toriyama: Tokyo med. Ztschr. **11**: No. 23, 1897.

In experimental guinea-pigs Ishiwara and others found swelling of the bitten area and lymph glands; acute inflammatory changes in the kidneys, hyperemia and hemorrhages of the suprarenals, hyperemia of the lungs and catarrh of the mucosa of the stomach. Ido[26] has found similar changes in guinea-pigs infected by the bite of rats. Futaki and his associates record swelling of the spleen, hyperemia, congestion and swelling of the liver, hemorrhages in kidneys and lungs of inoculated animals.

The blood changes have been reported by several writers. A leukocytosis occurs in most cases of rat bite fever, most marked during the attacks of fever. It usually reaches from 13,000 to 20,000 cells, and varies with the different attacks. In most cases the count returns almost to normal between paroxysms. The increase is often in the mononuclear cells, which may reach from 35 to 40 per cent. of the white count. However, others have reported a polymorphonuclear increase. Eosinophils have been found by some to reach from 5 to 15 per cent. In the case reported by me we found a leukocyte count of 16,000 one month after the bite of the rat, and during an attack of fever. The differential count showed 80 per cent. of polymorphonuclears, 4 per cent. of eosinophils; the rest were mononuclears. During the afebrile condition the white blood count dropped to 9,600 and rose again to 15,000 at the next attack.

There is usually a reduction in the red blood count with the development of the weakness and cachexia. The red count in most cases examined has been about four million, and the hemoglobin, proportionately reduced, about 80 per cent. Later an advanced anemia may develop.

The Wassermann test is of interest because of the close relationship of *Spirocheta morsus muris* to the *Spirocheta pallida*. Kitagawa and Mukoyama report a negative Wassermann in their case, and quote Kunusaki, who found the Wassermann negative in four of five cases of rat bite fever. They also quote Inada as obtaining a negative Wassermann in Weil's disease, a spirochete infection. On the other hand, Costa and Troisier, and Mauriac[27] obtained positive Wassermann in their cases. The Wassermann was negative in the case reported by me. It seems, therefore, that the Wassermann test is not to be depended on as an aid in the diagnosis of this disease. In cases with a positive reaction, syphilis must, of course, be considered, as in the case reported by Brennemann[28] in a child with indications of congenital syphilis, whose mother gave a positive test.

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26. Ido, Y., Ito, H., Wani, H., and Okuda, K.: Circulating Immunity Principles in Rat Bite Fever, J. Exper. M. **26**:377, 1917.
27. Mauriac, P.: Rat Bite Disease, J. de méd. de Bordeaux **89**:93, 1918.
28. Brennemann, J.: A Case of Rat Bite Fever, Surg. Clin. **2**:433, 1918.

DIAGNOSIS

The diagnosis of rat bite fever is based on:

1. History of bite by rat or other animal.
2. Cardinal symptoms, of which one or more are usually present.
   (a) Characteristic fever, usually relapsing.
   (b) Exanthem.
   (c) Muscular pains.
   (d) Nervous symptoms.
   (e) Lymphangitis and adenitis.
3. Demonstration of *Spirochaeta morsus muris*.
   (a) In blood during febrile attack.
   (b) In area of bite, skin lesions or enlarged lymph glands.
   (c) Animal inoculation, preferably mouse in which spirochetes can be demonstrated in blood in from five to fourteen days, or guinea-pig, etc.
4. Therapeutic test—administration of arsphenamin.

In the differential diagnosis we must consider (1) erysipelas; (2) pyogenic infection (phlegmon or pyemia or septicemia); (3) relapsing fever; (4) trench fever; (5) malaria; (6) syphilis; (7) erythema multiforme.

1. *Erysipelas.*—This disease can be differentiated by finding the streptococcus; absence of characteristic exanthem of rat bite fever; temperature curve; course of the disease.

2. *Pyogenic Infection.*—In rat bite fever blood culture is negative; absence of suppuration in the bite, unless secondary infection occurs; characteristic fever; incubation period; eruption; history of bite.

3. *Relapsing Fever.*—Finding of spirochete of Obermeyer; number of attacks rarely more than three; short incubation period.

4. *Trench Fever.*—Spread by body louse; fever, relapsing or irregular, or continuous; sudden onset like influenza; nystagmus on extreme lateral rotation of eyeballs; enlarged spleen, harder than that in typhoid; macular rash; shin pains; painful joints without swelling; no laboratory diagnosis at present. Caused by resistant filterable virus.

5. *Malaria.*—Blood examination (*Plasmodium malariae*); therapeutic test by use of quinin; enlarged spleen; endemic character of disease.

6. *Syphilis.*—History of infection; examination of lesion for *Spirocheta pallida;* Wassermann test; clinical manifestations.

7. *Erythema.*—Symmetrical arrangement of lesions; absence of history of external injury; recurrence of lesions; lesions of vivid color, often edematous; frequent association with rheumatism.

PROGNOSIS

The prognosis is usually favorable. The mortality has been about 10 per cent. The outcome depends on the severity of the disease. Cachexia, edema, nephritis, or severe anemia are bad signs. The patient is often incapacitated for a long time. The disease is more serious in very young or old people. A short incubation period followed by severe nervous manifestations usually indicates danger Death may occur during the first few attacks of fever from severe toxemia. As already stated, attacks of fever may occur for years after the bite. The average course of the disease is from two to three months. With the use of arsphenamin the prognosis is very favorable, the symptoms usually disappearing after one or two injections. No recurrences follow this treatment, as a rule.

TREATMENT

Prophylactic treatment consists of immediate cauterization of the bitten area with fuming nitric acid. The acid should be applied thoroughly in the bite, incision being done if necessary. Such treatment within an hour will usually prevent the disease and should be practiced in all animal bites. The ancient Japanese tried numerous odd cures, such as the use of poultices of herbs, filling the wound with gunpowder and then exploding it, applying raw meat and feeding it to a cat. Later reports have appeared in which quinin, iodid, salicylates and arsenic compounds by mouth were tried, but with no definite effect. In 1912, Hata[29] reported the use of arsphenamin in eight cases with complete recovery and disappearance of all symptoms in all but one case. Others have reported equally happy results. One or two injections usually suffice. The specific curative value of arsphenamin led Hata and others to suspect a spirochete as the cause of the disease. Mercury also seems to have a definite curative value (Borelli[30]). Arsphenamin has been found to have a curative value in experimentally inoculated animals. It should be given in all cases of rat bite fever.

REPORT OF CASE

Case.—An American boy, 9 years of age, was first seen by Dr. P. A. Gibbons, April 8, 1919. The history was as follows: March 25 the patient was bitten on the right index finger by a large gray rat while playing near his father's printing office. He reached his hand down into a barrel when the rat caught his finger, and according to the patient did not release its hold until it was killed by a person attracted by the screams of the boy. When the boy reached home the finger was painted with tincture of iodin. After

29. Hata, S.: Salvarsantherapie der Rattenbisskrankheit in Japan, München. med. Wchnschr. **59**:854, 1912.

30. Borelli, E.: Mercurial Treatment of Rat Bite Disease, Policlinico **25**: 25, 1918.

the bite he made no complaint and the wound seemed to heal nicely. On the fourteenth day he began to complain of pain in the finger and a burning sensation. The finger had become reddened and swollen. A physician was then called. He found the finger reddened, swollen, and at the site of the bite a slightly elevated blue red papule surrounded by a lighter edematous zone. The finger was painful on pressure. Examination revealed enlargement of the lymph glands in the right axilla. The supratrochlear glands were slightly enlarged. The physician made an incision but no pus was found. The area was swabbed with tincture of iodin. The boy returned to school the following day. Three days later (seventeen days after the bite) he complained of not feeling well, and the physician was again called and again incised the finger, finding very little pus. The symptoms were drowsiness, weakness, headache, diarrhea and vomiting. The gastric symptoms lasted for four days. April 11 the temperature was 102 F. The boy complained of chills and went to bed.

The patient was seen by me April 28. On this day his temperature was 99 F. He had suffered three attacks of fever, accompanied by severe headache, nausea and vomiting, pains in the back and extremities. These occurred at intervals of six days and lasted two to three days. During the third attack he became dizzy and fell. He was then sent to bed.

Physical Examination.—April 28. Patient was pale, rather thin and had an anxious look. Temperature, 99 F.; pulse, 90. The right index finger was bluish red, the color extending over the terminal phalanx. It was swollen and somewhat indurated. The incision had completely healed. On the right forearm were several bluish red, slightly elevated, well defined areas or nodules varying in size from a quarter to one inch in diameter. They were present on the flexor and extensor surface. Between them could be seen very faint reddish streaks. The supratrochlear glands were enlarged, measuring almost an inch in the greatest diameter. They were somewhat elastic and painful when compressed. The right axillary glands were also large, about the size of a walnut and not very hard. On questioning the patient and mother I learned that the skin nodules had first been seen about three weeks after the bite. A rash on the chest and abdomen was also reported to have been present. The rest of the body presented no eruption at this time. There was slight edema of the lower eyelids.

Heart and lungs: Negative.

Abdomen: Somewhat distended; suggesting slight ascites.

Liver: The lower edge was palpable along the free margin of the ribs, and flatness extended to the fifth interspace.

Spleen: Not enlarged.

Lymph glands: Right axillary glands enlarged, also supratrochlears. Other glands normal.

Head and neck: Negative.

Extremities: Negative, except for right arm already described.

Temperature: 99 F.; pulse, 90; respiration, normal.

Urine: Amount, normal; acid; clear; specific gravity, 1.025. Albumin: trace. Casts: a number of hyaline and granular; no red blood cells.

Blood Examination: April 28, 1919: Erythrocytes, 4,100,000; leukocytes, 16,000. Differential count: polymorphonuclears, 80 per cent.; mononuclears, 16 per cent.; eosinophils, 4 per cent.; hemoglobin (Sahli), 75 per cent.

Blood smears: Smears of blood obtained by puncture of the lobe of the ear were stained with Giemsa stain, Wright's stain, Jenner's stain and india ink April 29 when the temperature had dropped to 99 F. All examinations were negative.

Blood cultures: April 29, 10 c.c. of blood were drawn from the arm, and 3 c.c. were placed in 200 c.c. each of plain bouillon and glucose bouillon, and

an equal amount in glucose agar (50 c.c.) for plating. The cultures were all negative aerobically. Unfortunately pressure of other work prevented animal inoculations at this time.

May 2: Temperature, 98.6 F. Erythrocytes, 4,600,000; leukocytes, 9,600; polymorphonuclears, 70 per cent.; mononuclears, 27 per cent.; eosinophils, 3 per cent. Blood smears stained with Giemsa and Jenner stain were negative.

Patient feels much better, but complains of weakness and loss of appetite. The skin nodules are much smaller and have almost disappeared. The right axillary glands are still enlarged. No rash is present on the body.

May 10: I was called to see the patient who had a severe chill and high fever on the evening of May 9. Temperature, 101 F.; pulse, 100. The patient complained of nausea and severe headache. The nodules on the right arm were somewhat larger than on May 2, and pressure on the right axillary glands caused pain.

Blood examination: Erythrocytes, 4,400,000; leukocytes, 15,000; polymorphonuclears, 75 per cent.; mononuclears, 23 per cent.; eosinophils, 2 per cent.

Blood smears stained with Giemsa and Jenner failed to show any spirochetes after prolonged search. I inoculated two guinea-pigs with blood obtained from the left arm vein, using 3 c.c. intraperitoneally. The animals remained well for four weeks and showed no signs of illness whatever.

June 25: The patient felt much better but tired quickly. He complained of gastric disturbance. The nodules on the right arm had entirely disappeared. The right axillary glands were only slightly enlarged. The edema about the eyes had disappeared. The mother stated that the patient had lost about 20 pounds during his illness. From May 9 to June 25 the patient had two attacks of fever, but much less severe than the earlier attack and lasting only a day or two. I advised the administration of neoarsphenamin intravenously. The patient had been treated symptomatically and was given Fowler's solution, from 3 to 6 drops, three times a day.

September 30: The patient felt well. The glandular enlargement had disappeared, and the patient had been free from attacks since July 28, when his temperature rose to 101 F.

Blood examination: erythrocytes, 4,800,000; leukocytes, 9,000; polymorphonuclears, 76 per cent.; mononuclears, 22 per cent.; eosinophils, 2 per cent.

SUMMARY OF CASE

A boy, aged 9 years, was bitten on the right index finger by a rat, which instead of escaping, had to be killed in order to release its hold. The wound was shortly afterward painted with tincture of iodin and healed. After a period of fourteen days, inflammation, edema and induration occurred, accompanied by lymphangitis and lymphadenitis, and the appearance of a blue red exanthem. There were also high fever and chills, and gastric disturbances. This attack was followed by three others at intervals of about six days, each characterized by chills, fever, nausea, headache and pains in the extremities. Reappearance of the exanthem with these attacks was noted. There was marked lymphadenitis of the trochlear and axillary glands. The spleen was not enlarged. Slight nephritis existed. Blood examination revealed a leukocytosis, which reappeared with subsequent febrile attacks and returned almost to normal between paroxysms. Spirochetes or other organisms were not found in the peripheral blood, but the patient was not seen until thirty-four days after the bite. Inoculation of two guinea-pigs with blood obtained forty-six days after the bite proved negative. Cultures or animal inoculations were not obtained from the skin nodule or the local lymph glands. Blood smears made from the ear failed to reveal any spirochetes on several examinations, the first being made thirty-four days after the bite (twenty days after first paroxysm). The subsequent history reveals recurring attacks of fever at longer intervals, and less severe. No attack has occurred in the last two months.

The case is typical of rat bite fever, and of special interest because it calls attention to the presence of rats infected with the virus of the disease in this community. A study of rats for the presence of *Spirocheta morsus muris* is now under way.[31]

519 Front Street.

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THE PROTEIN AND LIPIN CONTENT OF BLOOD SERUM IN THE NEPHRITIDES

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The changes that the blood undergoes in renal disease have of recent years received much attention, especially since the methods for examination of small quantities of blood for the nonprotein nitrogen fractions have been very ingeniously improved by various American scientists. The estimation of functional capacity of the kidneys as well as the art of prognosis and diagnosis have been much aided by these investigations. It is noteworthy, however, how comparatively slight is the attention that has been paid to the protein and lipin fractions of the blood of nephritic patients.

The first reliable estimation of the serum proteins was made in 1845 by Becquerel and Rodier, who reported that the total protein content was lessened in cases of Bright's disease, cardiac disease with edema and severe puerperal affections. C. Schmidt found the protein content much increased in cholera and diminished in nephritic individuals.

In normal subjects, the ratio of serum albumin to serum globulin is approximately from 1.5 to 2.0: 1. It has been recorded by certain investigators that in chronic renal disease this ratio is markedly disturbed. In Table 1 an attempt has been made to gather from the literature the conflicting results reported. Mya and Viglezio summarized their findings as follows: In disease the albumin globulin ratio is much altered, the globulin increasing and the albumin diminishing. These alterations vary directly with those which occur in transudations. An increase of blood pressure increases the loss of albumin more than that of globulin. The investigations of von Limbeck and Pick and of Joachim seem to indicate that there is no disturbance in the albumin globulin ratio that should be especially characteristic of nephritis. Freund found that the globulin was reduced in nephritis.

In 1903, Erben reported that in chronic parenchymatous nephritis the globulin of the blood serum was much increased. But this did not seem to impress Morawitz, who, critically reviewing the literature on the subject in 1909, stated that no pathologic significance need be attached to the albumin globulin ratio changes in cases of nephritis. In this opinion, Ewing, von Noorden and others seem to concur.

TABLE 1.—Protein Estimations of Blood Serum by Various Authors

Author	Condition	Albumin	Globulin
Hammarsten	Normal	4.52	3.1
Patein	Normal	4.63	2.77
v. Limbeck and Pick	Normal	6.17-8.31	1.69-3.83
Rowe	Normal	5-6	1.6-1.7
Epstein	.....	4.662	2,738
Estelle	Chronic Bright's disease	5.44	3.06
	Chronic Bright's disease	3.6	1.8
v. Limbeck and Pick	Chronic nephritis	6.86	3.14
	Chronic nephritis	9.09	0.909
	Chronic nephritis	5.05	4.95
	Chronic nephritis	7.14	2.86
	Chronic nephritis	6.38	3.62
	Chronic nephritis	2.91	7.09
	Chronic nephritis	4.84	5.16
	Chronic nephritis	6.75	3.25
	Mediastinal tumor	6.41	3.59
	Hepatic cirrhosis	4.84	5.16
	Pneumonia	6.396	3.604
	Pneumonia	7.42	2.58
	Typhoid	6.15	3.85
	Febrile icterus	6.51	3.49
	Febrile icterus	8.28	1.72
	Pleurisy	2.60	7.40
	Erysipelas	6.21	3.79
	Meningitis	4.88	5.12
	Cancer of uterus	7.28	2.72
	Cancer of ovary	4.39	5.61
	Diabetes mellitus	5.56	4.44
	Diabetes mellitus	8.67	1.33
	Diabetes mellitus	8.32	1.68
	Diabetes mellitus	4.47	5.53
	Diabetes mellitus	4.61	5.39
	Diabetes mellitus	5.89	4.11
	Chlorosis	6.547	3.453
	Anemia	6.17	3.83
Erben	Subchronic nephritis	0.042	4.5317
	Chronic parenchymatous nephritis	0.2593	7.0352
	Contracted kidney	2.9042	2.5580
Cloetta	Eclampsia	3.42-5.21	1.86-2.31
Joachim	Chronic nephritis; uremia	6.238	3.761
	Chronic nephritis; uremia	5.327	4.672
	Cardiac disease	6.407	3.592
	Myocarditis	5.332	4.338
Freund	Pernicious anemia	.....	38%
	Bright's disease	.....	25 to 33%
Halliburton	Acute infectious fevers	.....	Increased
Duceschi	Thymectomy (dog)		
	Before convulsions	Increased	
	After convulsions	.....	Increased
Epstein	Cardiac disease	4.417	2.240
	Chronic interstitial nephritis	4.310	2.396
	Chronic parenchymatous nephritis	0.466	3.492
Burckhardt, Wallerstein, Lewinski, Githens	Starvation	.....	Increased
Meyer, Hurwitz and Taussig	Antitoxic immunity	.....	Increased
Rowe	Pneumonia	3.7	2.5
	Syphilis	5.0	2.5
	Chronic nephritis	3.9	2.4

In 1912 and 1913, Epstein published three papers recording the results of chemical studies on blood serums and puncture fluids. He concluded that the globulins were increased in cardiac disease associated with decompensation and serous effusions, in pulmonary and respiratory affections (inflammatory and noninflammatory), in diabetes mellitus and in chronic parenchymatous nephritis. So far as the last named disease is concerned, he definitely corroborated Erben's results, obtaining figures for the albumin globulin ratio which indicate the marked reduction of the albumin fraction and the enormous increase in globulin.

Based on his findings in nine cases of parenchymatous nephritis, in which, besides the globulin increase, he also found a huge amount of cholesterol in the serum, Epstein propounded his theory of the etiology of certain cases of chronic parenchymatous nephritis and of the causation of the edema in that disease. According to him, there is a group among the cases of chronic parenchymatous nephritis which is due to a constitutional disorder — of a metabolic or endocrinic nature — in which the renal or other manifestations are concomitant or secondary in point of development and importance. He does not, however, describe cases of chronic parenchymatous nephritis in which the protein or lipin fractions vary from the "metabolic" (*sic*) type, and which he should point out as "nonmetabolic" in nature.

He ascribes the edema to the following factor: "The loss of protein incurred by the blood serum through the continuous albuminuria causes a decrease in the osmotic pressure of the blood, which fact favors the absorption or imbibition and retention of the fluid by the tissues." The marked increase in the lipin content in these cases is taken as an evidence of the metabolic derangement of the organism, and to it is also ascribed some responsibility for the edema. On these findings, Epstein recommends for such patients a diet rich in proteins and poor in fats.

The theory of Epstein has points that are very appealing to the clinician who will venture anything to help his patient who has chronic edema. In practice, however, that group of which Epstein speaks, seems to be very rare. Of sixteen cases of chronic parenchymatous nephritis with marked edema and of seven with only slight edema, I have not found a single case which should have the marked protein and lipin deviations indicated by Epstein, or which should be benefited (in four of the cases in which the attempt was made) by a high protein, fat poor diet.

In the examination of the patients, the blood was drawn before breakfast, and the blood serum was examined for the proteins by the method described by Morawitz. The cholesterol was determined by the method of Autenrieth and Funk as described by Hawk.

TABLE 2.—SERUM ANALYSIS OF NORMAL HUMAN BEINGS

Case	Total Protein	Albumin	Globulin	Globulin, per Cent.	Cholesterol, Mg. per 100 C.c.
1	8.47	5.43	3.07	35	165
2	7.90	4.69	3.21	40	147
3	6.76	4.39	2.37	35	139
4	7.20	4.95	2.25	31	148

TABLE 3.—Serum Analysis in Acute and Chronic Interstitial Nephritis

Case	Total Protein	Albumin	Globulin	Globulin, per Cent.	Cholesterol, Mg. per 100 C.c.
Acute Nephritis					
1	5.86	3.62	2.24	38	157
2	7.15	4.37	2.78	38	162
3	6.79	4.14	2.65	39	139
4	7.96	4.25	3.71	46	185
5	7.76	3.96	3.80	48	167
6	7.65	4.73	2.92	38	160
Chronic Interstitial Nephritis					
7	8.67	4.89	3.78	43	220
8	7.42	4.37	3.05	41	180
9	7.06	4.44	2.62	37	175
10	6.53	3.88	2.65	40	164
11	7.07	4.32	2.75	38	210
12	8.06	5.73	2.93	34	193
13	7.53	4.86	2.67	35	139
14	7.74	4.59	3.15	40	148

TABLE 4.—Serum Analyses in Cases of Chronic Parenchymatous Nephritis

Case	Total Protein	Albumin	Globulin	Globulin, per Cent.	Cholesterol, Mg. per 100 C.c.
1	6.00	3.72	2.28	38	155
2	7.42	4.75	2.67	36	174
3	6.78	4.41	2.37	35	183
4	4.24	2.93	1.31	31	194
5	5.90	3.72	2.18	37	167
6	5.81	3.37	2.44	42	139
7	5.58	3.41	2.17	39	225
8	7.60	4.26	3.34	44	184
9	5.76	3.75	2.01	35	137
10	5.73	3.84	1.89	33	173
11	6.09	4.14	1.95	32	275
12	6.16	3.76	2.40	39	216
13	6.74	3.98	2.76	41	274
14	6.75	4.05	2.70	40	139
15	7.13	4.14	2.89	42	164
16	6.82	4.37	2.45	36	144
17	6.41	4.17	2.24	35	153
18	7.33	4.62	2.71	37	149
19	5.72	3.95	1.77	31	162
20	7.73	4.72	3.01	39	166
21	6.04	3.87	2.17	36	156
22	6.03	3.98	2.05	34	165
23	6.47	4.27	2.20	34	172

TABLE 5.—Serum Analyses in Other Diseases

Case	Diagnosis	Total Protein	Albumin	Globulin	Globulin, per Cent.	Cholesterol, Mg. per 100 C.c.
1	Pleurisy with effusion	6.40	4.16	2.24	35	175
2	Pleurisy with effusion	7.48	4.19	3.29	44	220
3	Pleurisy with effusion	7.85	4.32	3.53	45	185
4	Pleurisy with effusion	6.95	4.17	2.78	40	147
5	Portal obstruction	7.07	4.10	2.97	42	239
6	Portal obstruction	6.69	4.22	2.47	37	226
7	Cardiac disease with edema	7.17	4.16	3.01	42	194
8	Cardiac disease with edema	6.69	3.95	2.74	41	148
9	Cardiac disease with edema	6.86	4.12	2.74	40	220
10	Diabetes	6.82	4.16	2.66	39	183
11	Diabetes	7.62	4.42	3.20	42	138
12	Diabetes	6.69	3.95	2.74	41	195

Without going into any painstaking argumentation, it will be seen that there is no protein change in the condition of chronic parenchymatous nephritis which is characteristic of that disease and which does not occur in the other types of the nephritides and in other diseases. The cases of so-called nephrosis which Epstein describes must be very rare, and it is possible that he has culled the instances which he reports from an extremely large number of cases of chronic parenchymatous nephritis in which the albumin globulin ratio in the serum is not markedly disturbed. If so, he fails to mention how rare these nephrosis cases are, and he fails to record his results with cases of chronic parenchymatous nephritis that are not in the so-called "metabolic or endocrinic" group.[1] Several years ago,[2] I had the privilege of studying a patient who was suffering from nonparasitic chyluria, whose blood contained 320 mm. of cholesterol. The urine contained very much albumin and fat. On feeding this patient on a diet poor in fat, we were able to reduce the fat in the urine very markedly, and also to diminish somewhat the protein excretion. Is it possible that this was a type of case that Epstein describes, in whom the constant excretion of huge amounts of lipins so irritated the kidney epithelium as to induce the marked albumin excretion?

On feeding patients suffering with chronic parenchymatous nephritis a diet of whites of eggs, skimmed milk, peas and lean meat for several days it was observed (Table 6) that the albumin globulin ratio was not affected, though there was some increase in the total protein of the blood serum. The edema, however, did not diminish in the slightest degree.

TABLE 6.—Effect of Feeding a Protein Rich Diet in Cases of Chronic Parenchymatous Nephritis

Case	Period	Total Protein	Albumin	Globulin	Globulin, per Cent.
4	Before	4.24	2.93	1.31	31
	After	5.27	3.59	1.68	32
8	Before	7.60	4.26	3.34	44
	After	7.75	4.50	3.25	42
9	Before	5.76	3.75	2.01	35
	After	6.12	3.92	2.20	36
11	Before	6.09	4.14	1.95	32
	After	6.37	4.46	1.91	30

It has been pointed out by Kerr, Hurwitz and Whipple that "there is a remarkable stability of the blood serum protein level in widely varying conditions of health and disease." Feeding of protein seems not to affect to any extent the serum protein content. Böhme and Reiss have shown, by the refractometer, that the concentration of

1. A personal inquiry directed to Dr. Epstein regarding these points remained unanswered.

2. Kahn and Sanes: Arch. Int. Med. **17**:181 (Feb.) 1916.

serum protein is only slightly changed after a large meal, this change following no rule, being either an increase or a decrease (Rowe). The results of Rowe show that "after four days of high protein diet there is, on the average, a slight increase in the total proteins, [with] no definite division of this increase between the albumin and the globulin fractions."

So far as the cholesterol content of the serum is concerned, one can only say that while, in general, there is an increase of this lipin in the blood serum in cases of chronic parenchymatous nephritis, this is by no means a universal rule. It must also be observed that the cholesterol content is increased in certain other conditions, as, for example, in chronic interstitial nephritis, in diseases with serous effusions (at times), and in certain metabolic derangements.

CONCLUSIONS

1. In the series of cases investigated, I did not find one case of the so-called "metabolic or endocrinic" type of chronic parenchymatous nephritis, as reported by Epstein.

2. The albumin globulin ratio does not seem to be markedly disturbed by various diseases.

3. Feeding of patients suffering with chronic parenchymatous nephritis on a protein rich, fat poor diet is a rather risky undertaking.[3]

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3. The following references may also be consulted.

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